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(54) Title: PRODRUGS

(57) Abstract

A pharmaceutical compound or an intermediate therefor, having the formula: D*-Linker*$(R_2')_k$-R_2, where R_2 and R_2' (if present) is the amide or ester residue of an aliphatic amino acid, k is 0 or 1, D* is a Drug residue bearing an accessible function selected from amine, hydroxy and carboxy, or a group amenable to attachment to said accessible function, Linker* is an at least bifunctional linker comprising a first function bound to said accessible function spaced from a second function forming an amide or acyl bond with the aliphatic amino acid; wherein the compound is free from long chain fatty acid esters; and with the provisos that Linker* does not consist solely of alkoxy when the Drug comprises a lactamcarboxy or enolic hydroxy function and that the Drug is not a monohydric nucleoside.

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PRODRUGS

Technical Field

This invention relates to the field of prodrugs, that is novel derivatives of otherwise known and proven drugs which release that drug in active or pro-active form in vivo. The enzymatic and/or chemical cleavage of the compounds of the present invention occurs in such a manner that the parent drug is released and the moiety or moieties split off remain non-toxic or are metabolized so that non-toxic or acceptable amounts of metabolic products are produced.The present compounds thus modify the in vivo availability of the parent compound compared to what would be the case if the parent compound was to be administered itself. For instance the prodrugs of the invention may give higher bioavailabilities, varied bioavailability kinetics or bioavailabilities with a decreased interpersonal spread.

Background to the invention

WO97/30051 and WO 98/21223 describe prodrugs of nucleoside analogues comprising a fatty acid ester and an amino acid ester, optionally combined on a linker structure which is in turn bonded to the nucleoside. As shown in the examples of WO 97/30051, the presence of the fatty acid component was essential to good bioavailability.

J Med Chem 39 (1) 10-18 1996 describes a number of acyloxymethyl ethers of the enolic drug oxindole and indicate that the amino acyl variants have poorer bioaviailability that the mother substance.

J Med Chem 22 657-661 (1979) and DE 2112057 describe valyloxymethyl esters of lactamcarboxy functions of various penicillins although to our knowledge none have shown clinical promise.

Brief description of the invention

In a ccordance with a first aspect of the invention there are provided pharmaceutical compounds of the formula:

$$D^*\text{-Linker}^* (R_2')_k\text{-}R_2$$

where R_2 and R_2' (if present) is the amide or ester residue of an aliphatic amino acid,

k is 0 or 1,

D* is a Drug residue bearing an accessible function selected from amine, hydroxy and carboxy,

Linker* is an at least bifunctional linker comprising a first function bound to said accessible function spaced from a second function forming an amide or acyl bond with the aliphatic amino acid;

wherein the compound is free from long chain fatty acid esters; and with the provisos that Linker* does not consist solely of alkoxy when the Drug comprises a lactamcarboxy or enolic hydroxy function and that the Drug is not a monohydric nucleoside.

The invention further provides novel intermediates useful for derivatising accessible hydroxy, carboxy or amino functions of Drugs to prepare prodrugs as described in the foregoing paragraph. Certain of these novel intermediates are also useful for derivatising other functions on drugs, as described and claimed in our co-pending international application filed 30 March 1999 and claiming priority from SE 9801216-4.

A further aspect of the invention provides the use of a structure of the formula -Linker* $(R_2')_k$-R_2 as a prodrug moiety for a drug bearing an accesible hydroxy, carboxy or amino function.

By the use of the invention the pharmacokinetics of a broad range of orally administered drugs are enhanced, for instance by improving absolute bioavailability or by providing a more even release of the mother compound or by providing for a reduced interpersonal spread in pharmacokinetic performance. However the compounds of the invention are not limited to those based on orally administered

drugs as the prodrugs of the invention, when parenterally administered, provide enhanced pharmacokinetic performance, for instance by improving solubility, while still allowing for efficient release of the mother compound.

Drug residue as used in its conventional significance, that is implying that during linkage a hydrogen or hydroxy has been eliminated from an accessible amino, carboxy or hydroxy function on the Drug. The amine function on the Drug can be a primary amine ($-NH_2$) or a secondary amine (-NH-).

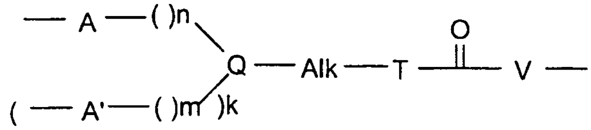
The expression difunctional in the context of the linker group means that the linker has at least one hydroxy or amine function available for esterification or amide bonding with R_2, or a carboxyl function available for amide bonding with the free α-amine function of R_2 . Spaced therefrom on the difunctional linker is a further functional group for linkage to a cooperating function on the Drug such as hydroxy, carboxy or amino.

The linker may in fact be trifunctional, that is the linker has at least three functions including two independently selected from hydroxy, amine or carboxy, the amine and hydroxy function(s) being available for esterification/amide bonding with the carboxyl functions of a pair of R_2, or the carboxy function(s) on the linker being available for amide bonding with the free α-amine function of R_2. These hydroxy/amine/carboxy functions are spaced from a further functional group for linkage with a cooperating hydroxy, carboxy or amine function on the drug. Other trifunctional linker groups may comprise a first hydroxy, amine or carboxy function cooperating with R_2, a function cooperating with the drug and a further functional group either underivatised such as hydroxy, carboxy, amine etc or alternatively protected with conventional pharmaceutically acceptable protecting groups.

The invention further provides pharmaceutical compositions comprising the pharmaceutical compounds of the invention and pharmaceutically acceptable carriers or diluents therefor. Additional aspects of the invention provide methods of medical treatment or prophylaxis comprising the administration of the pharmaceutical

compounds of the invention to a human or animal suffering from or prone to the ailment to which the respective Drug is applicable.

Convenient linker groups, for instance when the Drug comprises an amine or hydroxy function, include those of the Formulae IIa

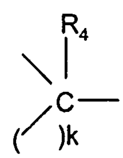


IIaa

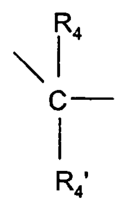
where A and A' are independently

an ester linkage between an hydroxy on the linker and the carboxy on R_2, or an amide linkage between an amine on the linker and a carboxy on R_2,

Q is a structure:



or

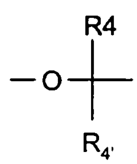


or Q is a monocyclic, saturated or unsaturated carbo- or heterocycle with 4, 5 or 6 ring atoms;

Alk is absent, C_1-C_4 alkylene or C_2-C_4 alkenylene;

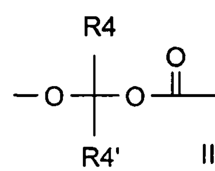
T is a bond, -O- or $-N(R_4)-$,

V is a bond or a structure of the formula IIbb or IIcc:



IIbb

or



IIcc

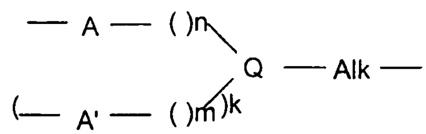
R_4 and R_4' are independently hydrogen or C_1-C_3 alkyl; and

m and n are independently 0, 1 or 2;

k is 0 (that is the branch is absent)or 1

A number of useful hetero or carbocycles for Q as a ring are defined below which is preferably an aromatic group such as pyridine, furyl, imidazol etc or especially phenyl, such as aromatic moieties wherein the arm(s) bearing the or each R_2 group are respectively para and meta or both meta to the remainder of the linker.

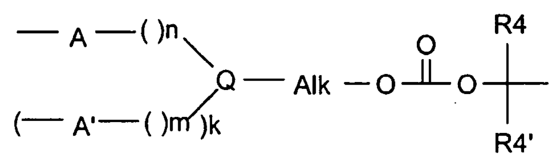
Where the Drug comprises a carboxyl function, the linker may comprise a structure of the formulae VIII:



VIII

where A, A', Q, Alk, k m, and n are as defined for Formula IIa.

Preferably, however, when the Drug comprises a carboxy function, the di- or trifunctional linker group is a structure of Formulae IId (that is a compound of Formulae IIa, wherein T is O and V is a structure of the formula IIbb):

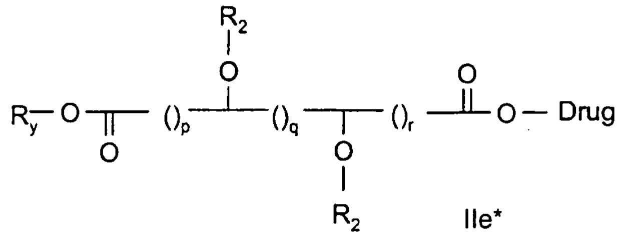


IIdd

In structure IId, R_4' is preferably hydrogen and R_4 is ethyl, phenyl, but especially methyl or hydrogen, or R_4 and $R_{4'}$ together define isopropyl.

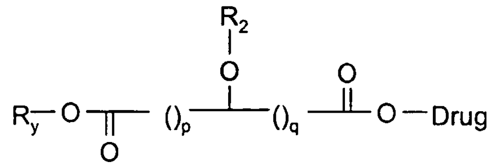
Particularly convenient structures when the drug comprises an hydroxy function include the corresponding structures to:

formula II e*, that is



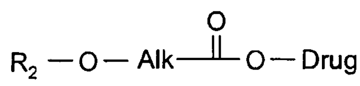
IIe*

formula II f*, that is



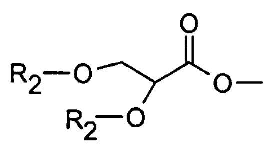
IIf*

Formula Id*, that is



Id*

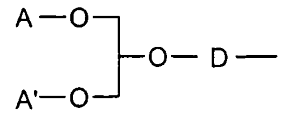
A favoured structure within formula IIa has the formula:



which breaks down in vivo to the nature identical glyceric acid. Particularly preferred are compounds derived from D-glyceric acid.

Thus preferred pharmaceutical compounds of the invention will comprise a [(R) 2,3-bis-(L-valyloxy)-propionyl] or [(R) 2,3-bis-(L-isoleucyloxy)-propionyl] moiety.

A preferred group of linker(R_2')-R_2 structures comprise glycerol derivatives of the formula IIc

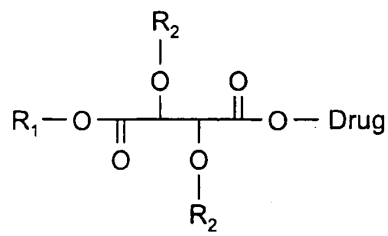


IIc

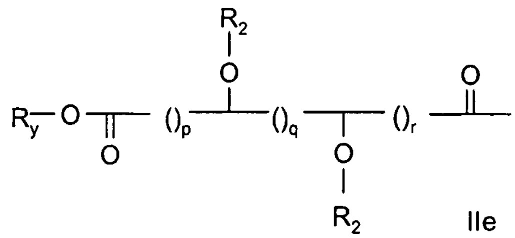
or the corresponding 2,3 enantiomer, where A is hydrogen or the acyl residue of an aliphatic L-amino acid ester, A' is the acyl residue of an aliphatic amino acid residue and D is a C_2-C_6 saturated or unsaturated dicarboxylic acid residue. Trifunctional linkers of the formula IIc are hydrolysed or otherwise break down in vivo to release the nature identical compounds glycerol, the L-amino acid, the fatty acid (if present) and the dicarboxylic acid, each of which are generally safely metabolised and/or excreted by the body. Preferably A and A' are both the same residue, particularly residues of L-valine or L-isoleucine.

Particularly preferred dicarboxylic acid residues include those derived from oxalic, malonic, tartronic, succinic, maleic, fumaric, malic, tartaric, glutaric, glutaconic, citraconic, itaconic, ethidine-malonic, mesaconic, adipic, allylmalonic, propylidenemalonic, hydromuconic, pyrocinchonic and muconic acids and the like. The dicarboxylic acid residue may be optionally substituted.

Several of the abovementioned dicarboxylic acids can themselves define a trifunctional linker. For instance hydroxy-substituted dicarboxylic acids such as tartaric acid or malic acid offer a number of configurations within the scope of the invention. Taking tartaric acid as an example a carboxyl function is available for esterification with an hydroxy function on the drug (optionally via a difunctional linker). The hydroxy function(s) are available for esterification with the respective carboxyl functions of the R_2 amino acid while the remaining carboxy group can be free, or optionally protected, for instance with a conventional pharmaceutically acceptable ester such as the methyl or ethyl ester.



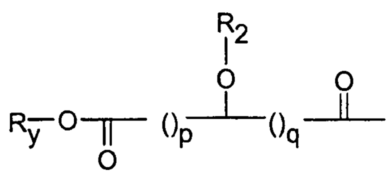
Favoured linkers of the tartaric acid series above can be generically depicted as Formula IIe:



IIe

where R_2 is as shown above, p, q and r are each independently 0 to 5, preferably 0 or 1 and R_y is the free acid, or a conventional pharmaceutically acceptable carboxy protecting group, such as the methyl, benzyl or especially the ethyl ester.

Favoured linkers of the malic series have the formula IIf:



IIf

where Ry, p,q and R_2 are as defined above, preferably those where p and q are zero.

Preferred pharmaceutical compounds of this aspect of the invention will hus comprise a moity selected from:

[3-methoxycarbonyl-2-valyloxy-propionyl],

[3-benzyloxycarbonyl-2-valyloxy-propionyl],

[3-methoxycarbonyl-2-isoleucloxy-propionyl],

[3-benzyloxycarbonyl-2-isoleucyloxy-propionyl],

[4-methoxycarbonyl-2,3-bis-valyloxy-butyryl],

[4-benzyloxycarbonyl-2,3-bis-valyloxy-butyryl],

[4-methoxycarbonyl-2,3-bis-isoleucyloxy-butyryl],

[4-benzyloxycarbonyl-2,3-bis-isoleucyloxy-butyryl],

And especially:

[3-ethoxycarbonyl-2-valyloxy-propionyl],

[3-ethoxycarbonyl-2-isoleucyloxy-propionyl]

[4-ethoxycarbonyl-2,3-bis-valyloxy-butyryl]

[4-ethoxycarbonyl-2,3-bis-isoleucyloxy-butyryl],

particularly those derived from L-malic acid and L-tartaric acid; and corresponding derivatives employing conventional pharmaceutically acceptable esters on the terminal carboxy function.

A further preferred prodrug moiety, especially for Drugs containing hydroxy groups which are not prone to electron withdrawal include α-ω hydroxyalkanoic acid derivatives where R_2 is esterified to the terminal hydroxy group. In these compounds hydrolysis and removal of the R_2 group in vivo leaves a reactive terminal radical which will tend to cyclize and prompt the effective release of the mother drug.Linkers of this aspect of the invention are conveniently prepared from α-hydroxy ω-carboxylic acids such as carbonic acid, glycollic acid, hydroxypropanoic acid, hydroxybutyric acid, hydroxyvaleric acid or hydroxycaproic acid.

Preferred pharmaceutical compounds will thus comprise a moiety selected from:

[3-(L-valyloxy)-propionyl]

[5-(L-valyloxy)-pentanoyl]

[5-(L-valyloxy)-cis-pent-2-enoyl]

[5-(L-valyloxy)-cis-pent-3enoyl]

[6-(L-valyloxy)-hexanoyl]

[3-(L-isoleuclyoxy)-propionyl]

[5-(L-isoleucyloxy)-pentanoyl]

[5-(L-isoleucyloxy)-cis-pent-2-enoyl]

[5-(L-isoleucyloxy)-cis-pent-2-enoyl]

[6-(L-isoleucyloxy)-hexanoyl]; and especially

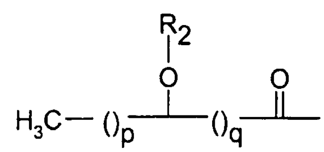
[4-(L-valyloxy)-butyryl];

[4-(L-valyloxy)-cis-but-2-enoyl]

[4-(L-isoleucyloxy)-butyryl]

[4-(L-isoleucyloxy)-cis-but-2-enoyl].

A convenient linker $(R_2')_k(R_2)$ structure has the formula:



IId

where R_2 is the residue of an aliphatic L-amino acid and, p is 0, 1 or 2-20 (optionally including a double bond) and q is 0-5, preferably 0.

Preferred pharmaceutical compound will thus comprise a moiety selected from:

[2-(L-valyloxy)-butyryl], [2-(L-isoleucyloxy)-butyryl],

[2-(L-valyloxy)-pentanoyl], [2-(L-isoleucyloxy)-pentanoyl],

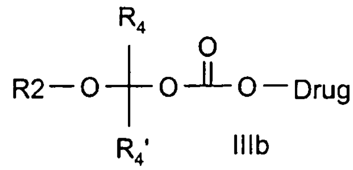
[2-(L-valyloxy)-hexanoyl], [2-(L-isoleucyloxy)-hexanoyl],

etc.

In formula IId, however, p and q are preferably 0, thus defining lactic acid derivatives, preferably L-lactic acid derivatives, such as the [2-(L-valyloxy)-propionyl] and [2-(L-isoleucyloxy)-propionyl] moieties, as the breakdown products, lactic acid and the amino aicd are both well accepted physiologically.

A convenient linker $(R_2')_k(R_2)$ structure, for instance with drugs comprising an hydroxy group prone to electron withdrawal has the formula:

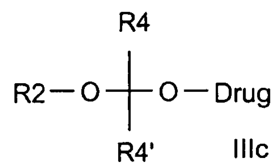
IIIb:



IIIb

where R_4 and R_4'are independently H or C_1-C_4 alkyl.

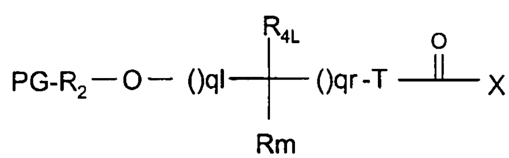
A convenient linker $(R_2')_k(R_2)$ structure for instance with hydroxy groups prone to electron withdrawing effects has the structure IIIc:



IIIc

where R_2, R_4 and $R_{4'}$ are as discussed above.

A preferred group of prodrugs of the invention have the formula:



wherein

PG-R_2 is the acyl residue of an aliphatic amino acid, optionally N-protected,

R_{4L} is H, C_{1-3} alkyl or phenyl,

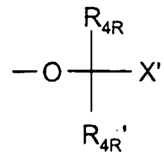
Rm is H, C_{1-3} alkyl, phenyl or -$()_m$-O-R_2

ql is 0-3, qr is 0-3, m is 0-2

T is a bond, -NR_4- or -O-

R_4 is H or C_{1-3}alkyl;

X is an ester linkage to a Drug bearing an accessible hydroxy function, an amide linkage to a Drug bearing an accessible amine function or a structure of the formula:



where

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl; and

X' is an ether linkage to a drug bearing an accessible hydroxy function or an ester linkage to a Drug bearing an accessible carboxy function;

and pharmaceutically acceptable salts thereof.

A further preferred group of compounds of the invention comprises those wherein Linker* $(R_2')_k$-R_2 comprises a structure of the formula

$$\text{PG-R}_2\text{—O—()ql—Ring—()qr-T—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—X}$$

wherein

PG-R_2 is the acyl residue of an aliphatic amino acid, optionally N-protected,

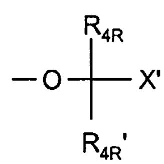
ql is 0-3, qr is 0-3,

T is a bond, -NR_4- or -O-

R_4 is H or C_{1-3}alkyl;

ring is an optionally substituted hetero- or carbocyclic ring structure,

X is an ester linkage to a Drug bearing an accessible hydroxy function, an amide linkage to a Drug bearing an accessible amine function or a structure of the formula:

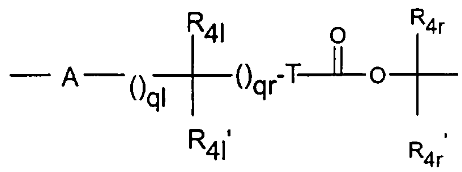


where

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl; and

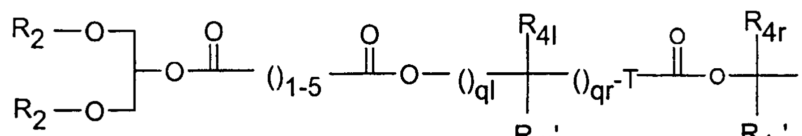
X' is an ether linkage to a drug bearing an accessible hydroxy function or an ester linkage to a Drug bearing an accessible carboxy function; and pharmaceutically acceptable salts thereof.

Preferably, the difunctional linker comprises a structure of the formula II"b:

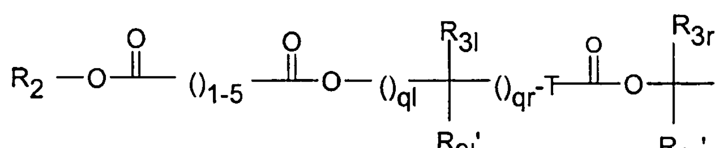


II"b

where T is a bond, -O- or -NH-, R_{4l} R_{4r} and R_{4l}' and R_{4r}' are independently H or C_1-C_3 alkyl and A is as defined above (or wherein A is a further difunctional linker to which one or more R_2 depend). Examples of structures belonging to the latter possibility for A include those of Formula Va and Vb:



Va



Vb

where T, q, R_2, R_{4l} R_{4l}' R_{4r} and R_{4r}' are as defined above. Although formulae Va and Vb depict the dicarboxylate moiety as unbranched, it will be apparent that a wide variety of dicarboxylates will be suitable here, including branched and/or unsaturated and/or substituted dicarboxylic acid derivatives or various lengths, as described in more detail above.

Amongst the preferred configurations for formulae II"b, Va and Vb, are those wherein T is absent.

Convenient values for the rightmost R_4 and $R_{4'}$ are hydrogen and for the left most R_4 and $R_{4'}$ both methyl. Other preferred embodiments comprise structures of the formulae II"b, Va or Vb wherein the rightmost R_4 is H and the rightmost R_4 is isopropyl, cycloC_{1-6}alkyl, phenyl or benzyl.

Convenient values of the leftmost q and rightmostq are as follows:

1,0;

2,0;

3,0; and

4,0;

Other convenient values include

1,1;

2,1;

3,1;

4,1; or

2,2.

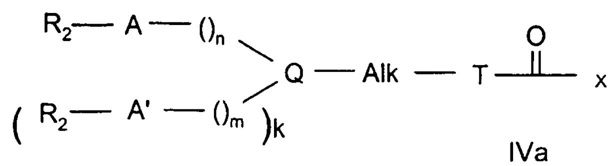
Especially 1,0; 2,0; 3,0; 1,1; 0,1; 2,2; 0,3; 3,1

Still further preferred embodiments comprise structures of the formula II"b, Va or Vb wherein T is -NH- or -O-.

Intermediates:

A further aspect of the invention provides novel intermediates for linking to Drugs having accessible amine, hydroxy or carboxy functions, but also including those drugs in our copending international application discussed above. However it should be appreciated that the pharmaceutical compounds of the invention are not limited to those prepared from the intermediates defined below, as many pharmaceutical compounds within the scope of the invention maybe synthesised by a stepwise process, for instance by first attaching an optionally protected di- or trifunctional linker to the drug, followed by attachment of the R_2 group(s). A number of such stepwise syntheses are exemplified below.

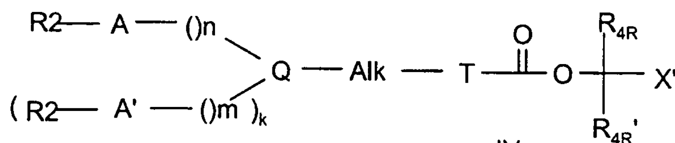
Preferred linkers in accordance with this aspect of the invention include compounds of the Formulae IVa:



IVa

where R_2, A, A', n, m, Q, Alk, k and T are as defined above and X is hydroxy or an activating group such as an acid derivatives including the acid halide, such as the chloride, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinamide derived esters, N-hydroxyphthalimide derived esters, N-hydroxy-5-norbornene- 2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like. Compounds of Formula IVa will be particularly useful for Drugs bearing hydroxy or amine functions.

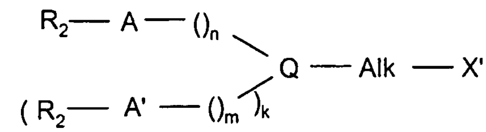
Further preferred linkers in accordance with this aspect of the invention include compounds of the formulae IVe:



IVe

where R_2, A, A', n, m, Q, Alk and T are as defined above, and R_4 an activating group such as a halide, including bromo, chloro and iodo. Compounds of Formula IVe will be especially useful for Drugs bearing carboxy functions (especially those where T is O, R_3 is Me and R_3' is H)

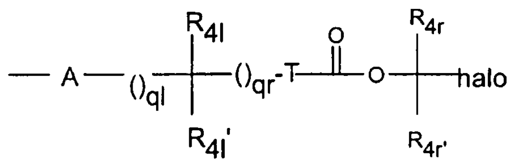
Alternative preferred di- or trifunctional linker compounds of this aspect of the invention include compounds of the Formulae IIIa:



IIIa

where R_2, A, A', n, m, Q and Alk are as defined above and R_4 is hydroxy or an activating moiety such as halo, including chloro, iodo and bromo.

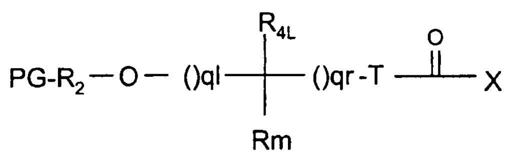
A preferred group of novel intermediates useful in applying structures of the formulae II"b to a drug and having the formula N-1:



N-1

where A, q, R_4, R_4' and T are as defined for formula II"b.

A preferred group of intermediates have the formula:



wherein

PG-R_2 is the acyl residue of an aliphatic amino acid, optionally N-protected,

R_{4L} is H, C_{1-3} alkyl or phenyl,

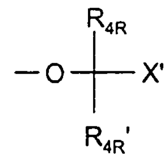
Rm is H, C_{1-3} alkyl, phenyl or -$()_m$-O-R_2

ql is 0-3, qr is 0-3, m is 0-2

T is a bond, -NR_4- or -O-

R_4 is H or C_{1-3}alkyl;

X is OH or an activating group or a structure of the formula:

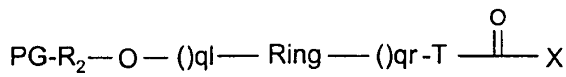


where

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl; and

X' is halo.

An alternative group of intermediates of the invention comprise a structure of the formula



wherein

PG-R_2 is the acyl residue of an aliphatic amino acid, optionally N-protected,

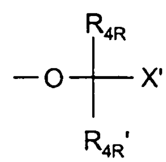
ql is 0-3, qr is 0-3,

T is a bond, -NR_4- or -O-

R_4 is H or C_{1-3}alkyl;

ring is an optionally substituted hetero- or carbocyclic ring structure,

X is OH or an activating group, such as halo, or a structure of the formula:



where

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl; and

X' is halo.

Halo for X or X' is bromo, chloro and especially iodo.

Representative intermediates of the invention include:

2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid iodomethyl ester

3,3- bis (N-CBz-L-valyloxymethyl)-propionic acid iodomethyl ester,

2-(N-CBz-L-valyloxy)ethoxycarbonyloxymethyl iodide

Iodomethyl 1,3-bis(N-benzyloxycarbonyl-L-valyloxy)-2-propyl carbonate,

Iodomethyl 2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionate,

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-DL-propionate.

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)isobutyrate.

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

Iodomethyl 2-O-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate

Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate.

Iodomethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate

2-(N-CBz-L-valyloxy)-ethyl iodomethyl carbonate

4-(N-CBz-L-valyloxy) butyric acid iodomethyl ester

Iodomethyl-3-(N-benzyloxycarbonyl-L-valyloxy)-benzoate

Iodomethyl-3-(N-benzyloxycarbonyl-L-valyloxy)-propionate

1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl 1-iodoethyl carbonate

3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethylpropyl iodomethyl carbonate

Iodomethyl 3,4-di-(N-CBZ-L-valyloxy)hydrocinnamate

3-(N-CBZ-L-valyloxy)phenyl iodomethyl carbonate

Iodomethyl 2-(N-CBZ-L-valyloxy)phenylacetate

Iodomethyl 4-(N-CBZ-L-valyloxyxy)phenylacetate

Iodomethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl) benzoate

Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy)cyclohexanoate.

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyrate

2-(N-(iodomethoxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane

1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester

Iodomethyl 5-[(*N*-benzyloxycarbonyl-L-valyloxy)methyl]-2-furoate

Iodomethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy)-benzoic acid

2,2-dimethyl-3-(N-Boc-L-isoleucyloxy)propionic acid iodomethyl ester

3,3- bis (N-CBz-L-isoleucyloxymethyl)-propionic acid iodomethyl ester,

2-(N-CBz-L-isoleucyloxy)ethoxycarbonyloxymethyl iodide

Iodomethyl 1,3-bis(N-benzyloxycarbonyl-L-isoleucyloxy)-2-propyl carbonate,

Iodomethyl 2-methyl-2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl) propionate,
Iodomethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxy)-DL-propionate.
Iodomethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxy)isobutyrate.
Iodomethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxy)-3-methyl-(S)-(+)-butyrate.
Iodomethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxy)-2-phenyl-DL-acetate
Iodomethyl 4-(N-benzyloxycarbonyl-L-isoleucyloxy) benzoate.
Iodomethyl 5-(N-CBz-L-isoleucyloxy)-2,2-dimethylvalerate
2-(N-CBz-L-isoleucyloxy)-ethyl iodomethyl carbonate
4-(N-CBz-L-isoleucyloxy) butyric acid iodomethyl ester
Iodomethyl-3-(N-benzyloxycarbonyl-L-isoleuclyloxy)-benzoate
Iodomethyl-3-(N-benzyloxycarbonyl-L-isoleucyloxy)-propionate
1,3-bis(*N*-tert-butoxycarbonyl-L-isoleucyloxy)-2-propyl 1-iodoethyl carbonate
3-(*N*-benzyloxycarbonyl-L-isoleucyloxy)-2,2-dimethylpropyl iodomethyl carbonate
Iodomethyl 3,4-di-(N-CBz-L-isoleucyloxy)hydrocinnamate
3-(N-CBz-L-isoleucyloxy)phenyl iodomethyl carbonate
Iodomethyl 2-(N-CBz-L-isoleucyloxy)phenylacetate
Iodomethyl 4-(N-CBz-L-isoleucyloxy)phenylacetate
Iodomethyl 4-(2-N-benzyloxycarbonyl-L-isoleucyloxyethyl) benzoate
Iodomethyl 4-(N-benzyloxycarbonyl-L-isoleucyloxy)cyclohexanoate,
Iodomethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-ethyl butyrate,
2-(N-(iodomethoxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-isoleucyloxy)-propane,
1-(2-N-CBz-L-isoleucyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester
iodomethyl 5-[(*N*-benzyloxycarbonyl-L-isoleucyloxy)methyl]-2-furoate
iodomethyl 4-(2-N-benzyloxycarbonyl-L-isoleucyloxyethoxy)-benzoic acid
and the corresponding chloro analogues.

Other preferred intermediates include:
2,2-dimethyl-3-(N-PG-L-valyloxy)propionic acid
3,3- bis (N-PG-L-valyloxymethyl)-propionic acid,
2-methyl-2-(N-PG-L-valyloxymethyl) propionate,
2-(N-PG-L-valyloxy)-DL-propionate.

2-(N-PG-L-valyloxy)isobutyrate.

2-(N-PG-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

2-O-(N-PG-L-valyloxy)-2-phenyl-DL-acetate

5-(N-PG-L-valyloxy)-2,2-dimethylvalerate

4-(N-PG-L-valyloxy) butyric acid

3-(N-PG-L-valyloxy)-propionate

2-(N-PG-L-valyloxymethyl)-2-ethyl butyrate

2,2-dimethyl-3-(N-PG-L-isoleucyloxy)propionic acid

3,3- bis (N-PG-L-isoleucyloxymethyl)-propionic acid

2-methyl-2-(N-PG-L-isoleucyloxymethyl) propionate,

2-(N-PG-L-isoleucyloxy)-DL-propionate.

2-(N-PG-L-isoleucyloxy)isobutyrate.

2-(N-PG-L-isoleucyloxy)-3-methyl-(S)-(+)-butyrate.

2-(N-PG-L-isoleucyloxy)-2-phenyl-DL-acetate

5-(N-PG-L-isoleucyloxy)-2,2-dimethylvalerate

4-(N-PG-L-isoleucyloxy) butyric acid

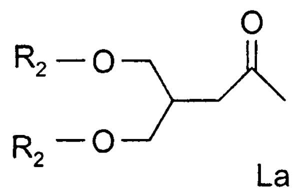
3-(N-PG-L-isoleucyloxy)-propionate

and the corresponding activated acid halides

where PG is an N-protecting group.

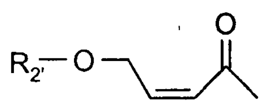
Exemplary Linker groups also include an alkoxy moiety such as $-CH_3O-$, $-CH(CH_3)O-$, $C(CH_3)_2O-$ and the like. Other exemplary L groups include an alkoxyalkoxy moiety such as $-CH_3O$-Alk-O-, $-CH(CH_3)O$-Alk-O-, $C(CH_3)_2O$-Alk-O, where Alk is a C_1-C_6 branched or straight chain saturated or unsaturated alkylene group, such as methylene, ethylene, 1,1bismethylethylene and the like. Other exemplary L groups include derivatives of hydroxyalkanoic acids, where the carboxy function is acylated to the hydroxy function at the 3 or 4 position of the backbone of the structure of formula III', while the hydroxy function is available for acylation with the carboxy function of the amino acid group R_2. Convenient hydroxyalkanoic acids include those derived from α-hydroxy ω-carboxylic acids such as carbonic acid, glycollic acid, hydroxypropanoic acid, hydroxybutyric acid, hydroxyvaleric acid or hydroxycaproic acid.

Linkers prepared from ω-hydroxybutyric derivatives are convenient as with these compounds hydrolysis and removal of the R_2 group in vivo leaves a reactive terminal radical which will tend to cyclize and prompt the effective release of the mother compound. Similarly, linkers of the formula L_a:



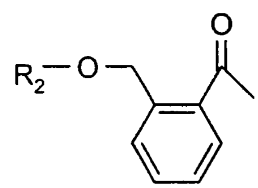
La

are convenient as enzymatic or spontaneous hydrolysis of a first of the R_2 groups will result in an active terminus able to curl back and attack the acyl linkage to the mother compound thus promoting spontaneous release of the linker fragment. Other convenient linkers along the same principle have the formula L_b or L_c:



L_b

or



L_c

Preferred novel intermediates thus include the free or activated acid precursors of compounds such as:

3-N-Boc-L-valyloxypropanoic acid, 3-N-Fmoc-L-valyloxypropanoic acid, 3-N-CBZ-L-valyloxypropanoic acid, 3-N-Boc-L-isoleucyloxypropanoic acid, 3-N-Fmoc-L-isoleucyloxypropanoic acid, 3-N-CBZ-L-isoleucyloxypropanoic acid, 4-N-Boc-L-valyloxybutyric acid, 4-N-Fmoc-L-valyloxybutyric acid, 4-N-CBZ-L-valyloxybutyric acid, 4-N-Boc-L-isoleucyloxybutyric acid, 4-N-Fmoc-L-isoleucyloxybutyric acid, 4-N-CBZ-L-isoleucyloxybutyric acid and the like; and the activated derivatives, such as the acid halides

Further useful intermediates comprise compounds such as

2-(L-valyloxy)propanoic acid, 2-(N-Boc-L-valyloxy)propanoic acid, 2-(N-Fmoc-L-valyloxy)propanoic acid, 2-(N-CBZ-L-valyloxy)propanoic acid, 2-(L-

isoleucyloxy)propanoic acid, 2-(N-Boc-L-isoleucyloxy)propanoic acid, N-(Fmoc-L-isoleucyloxy)propanoic acid, N-(CBZ-L-isoleucyloxy)propanoic acid,

2-(L-valyloxy)butyric acid, 2-(N-Boc-L-valyloxy)butyric acid, 2-(N-Fmoc-L-valyloxy)butyric acid, 2-(N-CBZ-L-valyloxy)butyric acid, 2-(L-isoleucyloxy)butyric acid, 2-(N-Boc-L-isoleucyloxy)butyric acid, N-(Fmoc-L-isoleucyloxy)butyric acid, N-(CBZ-L-isoleucyloxy)butyric acid, and the like; and activated derivatives therof, such as the acid halides.

Further novel intermediates include precursors of compounds of the formula IIe and IIf above, especially those derived from "natural" configurations such as L-malic and L-tartaric acid; for instance:

3-ethoxycarbonyl-2-valyloxy-propionic acid
3-ethoxycarbonyl-2-isoleucyloxy-propionic acid
4-ethoxycarbonyl-2,3-bis-valyloxy-butyric acid
4-ethoxycarbonyl-2,3-bis-isoleucyloxy-butyric acid
3-t-butoxycarbonyl-2-valyloxy-propionic acid
3-t-butoxycarbonyl-2-isoleucyloxy-propionic acid
4-t-butoxycarbonyl-2,3-bis-valyloxy-butyric acid
4-t-butoxycarbonyl-2,3-bis-isoleucyloxy-butyric acid
3-benzyloxycarbonyl-2-valyloxy-propionic acid
3-benzyloxycarbonyl-2-isoleucyloxy-propionic acid
4-benzyloxycarbonyl-2,3-bis-valyloxy-butyric acid
4-benzyloxycarbonyl-2,3-bis-isoleucyloxy-butyric acid, and the like;

especially the corresponding compounds wherein the amino acid is N-protected, particularly with a protecting group allowing selective deprotection of the N-protective group without removal of the carboxy protecting group; and the corresponding activated derivatives such as the acid halides.

Further useful intermediates include:

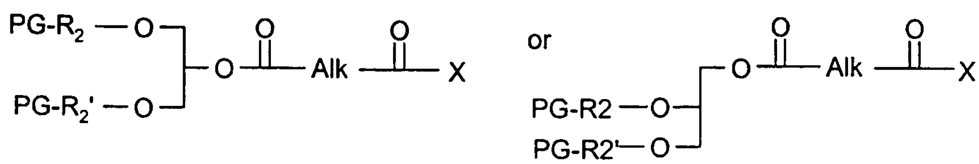
Still further novel intermediates include precursors corresponding to structure IId, such as;

2-(L-valyloxy)propanoic acid, 2-(N-Boc-L-valyloxy)propanoic acid, 2-(N-Fmoc-L-valyloxy)propanoic acid, 2-(N-CBZ-L-valyloxy)propanoic acid, 2-(L-isoleucyloxy)propanoic acid, 2-(N-Boc-L-isoleucyloxy)propanoic acid, N-(Fmoc-L-isoleucyloxy)propanoic acid, N-(CBZ-L-isoleucyloxy)propanoic acid, 2-(L-valyloxy)butyric acid, 2-(N-Boc-L-valyloxy)butyric acid, 2-(N-Fmoc-L-valyloxy)butyric acid, 2-(N-CBZ-L-valyloxy)butyric acid, 2-(L-isoleucyloxy)butyric acid, 2-(N-Boc-L-isoleucyloxy)butyric acid, N-(Fmoc-L-isoleucyloxy)butyric acid, N-(CBZ-L-isoleucyloxy)butyric acid, and the like; and activated derivatives therof, such as the acid halides.

Alkylation of the mother compound, for instance when group linker-$(R_2')_k$-R_2 such as L-R_y is derived from an alkoxyamino acid ester, is conveniently done with the corresponding N-protected haloalkoxyamino acid ester. Convenient alkylation intermediates thus include

iodomethyloxy-N-CBz-valyl,
iodomethyloxy-N-Boc-valyl,
iodomethyloxy-N-Fmoc-valyl
iodomethyloxy-N-CBz-isoeucyl,
iodomethyloxy-N-Boc-isoleucyl,
iodomethyloxy-N-Fmoc-isoleucyl,
and corresponding derivatives bearing other N-protecting groups.

Further useful intermediates include structures of the formula:



where Alk is C_1-C_4 alkylene or C_2-C_4 alkenylene and X is OH or an activating group.

Preferred intermediates of the above structure thus include:

malonic acid 2,3-*bis*-(L-valyloxy)-propyl ester,
malonic acid 2,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester,
malonic acid 2,3-*bis*-(N-Fmoc-L-valyloxy)-propyl ester,
malonic acid 2,3-*bis*-(N-Boc-L-valyloxy)-propyl ester,
malonic acid 2,3-*bis*-(L-isoleucyloxy)-propyl ester,
malonic acid 2,3-*bis*-(N-CBZ-L-isoleucyloxy)-propyl ester,
malonic acid 2,3-*bis*-(N-Fmoc-L-isoleucyloxy)-propyl ester,
malonic acid 2,3-*bis*-(N-Boc-L-isoleucyloxy)-propyl ester,
succinic acid 2,3-*bis*-(L-valyloxy)-propyl ester,
succinic acid 2,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester,
succinic acid 2,3-*bis*-(N-Fmoc-L-valyloxy)-propyl ester,
succinic acid 2,3-*bis*-(N-Boc-L-valyloxy)-propyl ester,
succinic acid 2,3-*bis*-(L-isoleucyloxy)-propyl ester,
succinic acid 2,3-*bis*-(N-CBZ-L-isoleucyloxy)-propyl ester,
succinic acid 2,3-*bis*-(N-Fmoc-L-isoleucyloxy)-propyl ester,
succinic acid 2,3-*bis*-(N-Boc-L-isoleucyloxy)-propyl ester,
glutaric acid 2,3-*bis*-(L-valyloxy)-propyl ester,
glutaric acid 2,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester,
glutaric acid 2,3-*bis*-(N-Fmoc-L-valyloxy)-propyl ester,
glutaric acid 2,3-*bis*-(N-Boc-L-valyloxy)-propyl ester,
glutaric acid 2,3-*bis*-(L-isoleucyloxy)-propyl ester,
glutaric acid 2,3-*bis*-(N-CBZ-L-isoleucyloxy)-propyl ester,
glutaric acid 2,3-*bis*-(N-Fmoc-L-isoleucyloxy)-propyl ester,
glutaric acid 2,3-*bis*-(N-Boc-L-isoleucyloxy)-propyl ester,
and the corresponding acid halides, in particular the chloride, acid anhydrides and triesters of each of the above, for instance
succinic acid 2,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester,4-methoxybenzyl ester
succinic acid 2,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester, 1,1-dimethylethyl ester, etc.

A particularly preferred group of intermediates within the above structure include:
malonic acid 1,3-*bis*-(L-valyloxy)-propyl ester,

malonic acid 1,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester,
malonic acid 1,3-*bis*-(N-Fmoc-L-valyloxy)-propyl ester,
malonic acid 1,3-*bis*-(N-Boc-L-valyloxy)-propyl ester,
malonic acid 1,3-*bis*-(L-isoleucyloxy)-propyl ester,
malonic acid 1,3-*bis*-(N-CBZ-L-isoleucyloxy)-propyl ester,
malonic acid 1,3-*bis*-(N-Fmoc-L-isoleucyloxy)-propyl ester,
malonic acid 1,3-*bis*-(N-Boc-L-isoleucyloxy)-propyl ester,
succinic acid 1,3-*bis*-(L-valyloxy)-propyl ester,
succinic acid 1,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester,
succinic acid 1,3-*bis*-(N-Fmoc-L-valyloxy)-propyl ester,
succinic acid 1,3-*bis*-(N-Boc-L-valyloxy)-propyl ester,
succinic acid 1,3-*bis*-(L-isoleucyloxy)-propyl ester,
succinic acid 1,3-*bis*-(N-CBZ-L-isoleucyloxy)-propyl ester,
succinic acid 1,3-*bis*-(N-Fmoc-L-isoleucyloxy)-propyl ester,
succinic acid 1,3-*bis*-(N-Boc-L-isoleucyloxy)-propyl ester,
glutaric acid 1,3-*bis*-(L-valyloxy)-propyl ester,
glutaric acid 1,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester,
glutaric acid 1,3-*bis*-(N-Fmoc-L-valyloxy)-propyl ester,
glutaric acid 1,3-*bis*-(N-Boc-L-valyloxy)-propyl ester,
glutaric acid 1,3-*bis*-(L-isoleucyloxy)-propyl ester,
glutaric acid 1,3-*bis*-(N-CBZ-L-isoleucyloxy)-propyl ester,
glutaric acid 1,3-*bis*-(N-Fmoc-L-isoleucyloxy)-propyl ester,
glutaric acid 1,3-*bis*-(N-Boc-L-isoleucyloxy)-propyl ester,
and the corresponding acid halides, in particular the chloride, acid anhydrides and diesters of each of the above, for instance
succinic acid 1,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester,4-methoxybenzyl ester
succinic acid 13-*bis*-(N-CBZ-L-valyloxy)-propyl ester, 1,1-dimethylethyl ester,
etc.

<u>Drugs</u>

Representative drugs having carboxyl functional groups include;
angiotensin-converting enzyme inhibitors such as alecapril, captopril, 1-[4-carboxy-2-methyl-2R,4R-pentanoyl]-2,3-duhydro-2S-indole-2-carboxylic acid, enalaprilic

acid, lisinopril, N-cyclopentyl-N-[3-[(2,2-dimethyl-1-oxopropyl)thio]-2-methyl-1-oxopropyl]glycine, pivopril, (2R, 4R)-2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid, (S) benzamido-4-oxo-6-phenylhexenoyl-2-carboxypyrrolidine, [2S-1[R*(R*))]] 2α, 3αβ, 7αβ]-1[2-[[1-carboxy-3-phenylpropyl]-amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid, [3S-1[R*(R*))]], 3R*]-2-[2-[[1-carboxy-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolone carboxylic acid and tiopronin;

cephalosporin antibiotics such as cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazuflur, cefazolin, cefbuperazone, cefmenoxime, cefmetazole, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotefan, cefotiam, cefoxitin, cefpimizole, cefpirome, cefroxadine, cefsulodin, cefpiramide, ceftazidime, ceftezole, ceftizoxime, ceftriaxone, cefuroxime, cephacetrile, cephalexin, cephaloglycin, cephaloridine, cephalosporin, cephanone, cephradine and latamoxef;

penicillins such as amoxycillin, ampicillin, apalcillin, azidocillin, azlocillin, benzylpencillin, carbenicillin, carfecillin, carindacillin, cloxacillin, cyclacillin, dicloxacillin, epicillin, flucloxacillin, hetacillin, methicillin, mezlocillin, nafcillin, oxacillin, phenethicillin, piperazillin, sulbenicllin, temocillin and ticarcillin;

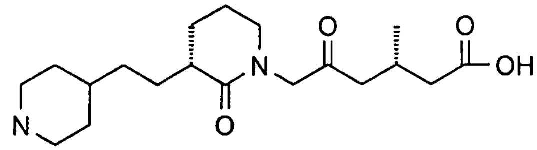
non-steroidal antiinflammatory agents such as acametacin, alclofenac, alminoprofen, aspirin (acetylsalicylic acid), 4-biphenylacetic acid, bucloxic acid, carprofen, cinchofen, cinmetacin, clometacin, clonixin, diclenofac, diflunisal, etodolac, fenbufen, fenclofenac, fenclosic acid, fenoprofen, ferobufen, flufenamic acid, flufenisal, flurbiprofin, fluprofen, flutiazin, ibufenac, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, lonazolac, loxoprofen, meclofenamic acid, mefenamic acid, 2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)propionic acid, naproxen, nifluminic acid, O-(carbamoylphenoxy)acetic acid, oxoprozin, pirprofen, prodolic acid, salicylic acid, salicylsalicylic acid, sulindac, suprofen, tiaprofenic acid, tolfenamic acid, tolmetin and zopemirac;

prostaglandins such as ciprostene, 16-deoxy-16-hydroxy-16-vinyl prostaglandin E_2, 16, 16-dimethylprostaglandin E_2, epoprostostenol, meteneprost, nileprost, prostacyclin, prostaglandins E_1, E_2, or $F_{2\alpha}$ and thromboxane A_2;

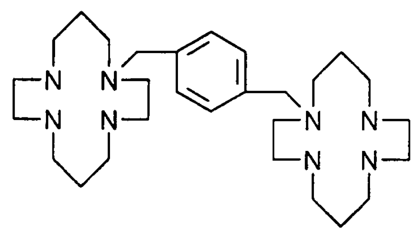
quinolone antibiotics such as acrosoxacin, cinoxacin, ciprofloxacin, enoxacin, flumequine, naladixic acid, norfloxacin, ofloxacin, oxolinic acid, pefloxacin, pipemidic acid and piromidic acid.

Representative drugs containing amine groups include:
acebutalol, albuterol, alprenolol, atenolol, bunolol, butopamine, butoxamine, carbuterol, cartelolol, colterol, deterenol, dexpropanolol, diacetolol, dobutamine, exaprolol, exprenolol, fenoterol, fenyripol, labotolol, levobunolol, metolol, metaproterenol, metoprolol, nadolol, pamatolol, penbutalol, pindolol, pirbuterol, practolol, prenalterol, primidolol, prizidilol, procaterol, propanolol, quinterenol, rimiterol, ritodrine, solotol, soterenol, sulfiniolol, sulfinterol, sulictidil, tazaolol, terbutaline, timolol, tiprenolol, tipridil, tolamolol, thiabendazole,
albendazole, albutoin, alinidine, alizapride, amiloride, aminorex, aprinocid, cambendazole, cimetidine, clonidine, cyclobenzadole, etintidine, fenbendazole, fenmetazole, flubendazole, fludorex, lobendazole, mebendazole, metazoline, nocodazole, oxfendazole, oxibendazole, oxmetidine, parbendazole, ranitidine, tetrahydrazoline, tiamenidine, tinazoline, tiotidine, tolazoline, tramazoline, xylometazoline,
dimethoxyphenethylamine, N-[3(R)-[2-piperidin-4-yl)ethyl]-2-piperidone-1-yl]acetyl-3(R)-methyl-β-alanine
adrenolone, aletamine, amidephrine, amphetamine, aspartame, bamethan, betahistine, clorprenaline, chlortermine, dopamine, ephrinephrine etryptamine, fenfluramine, methyldopamine, norepinephrine, tocainide
enviroxime, nifedipine, nimodipine, triamterene,
norfloxacin and similar compounds such as pipedemic acid, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-napthyridine-3-carboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazinyl)-3-quinolinecarboxylic acid.

A favoured amine drug, [[3(R)-2-piperidin-4-ylethyl)-2-oxopiperidinyl]acetyl]-3(R)-methyl-β-alanine (also known as L-734,217) has the formula:



A further preferred amino drug are the bicyclam anti HIV agents, such as AMD 3100:



Representative drugs containing hydroxy groups include:

steroidal hormones such as allylestrenol, cingestol, dehydroepiandrosteron, dienostrol, diethylstilbestrol, dimethisteron, ethyneron, ethynodiol, estradiol, estron, ethinyl estradiol, ethisteron, lynestrenol, mestranol, methyl testosterone, norethindron, norgestrel, norvinsteron, oxogeston, quinestrol, testosteron and tigestol;

tranquilizers such as dofexazepam, hydroxyzin, lorazepam and oxazepam;

neuroleptics such as acetophenazine, carphenazine, fluphenazine, perphenyzine and piperaetazine;

cytostatics such as aclarubicin, daunorubicin, dihydro-5-azacytidine, doxorubicin, epirubicin, estramustin, etoposide, 7-hydroxychlorpromazin, neplanocin A, pentostatin, podophyllotoxin, vinblastin, vincristin, vindesin;

hormones and hormone antagonists such as buserilin, gonadoliberin, icatibrant and leuprorelin acetate;

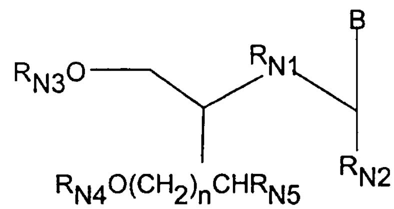
antihistamines such as terphenadine;

analgesics such as diflunisal, naproxol, paracetamol, salicylamide and salicyclic acid;

antibiotics such as azidamphenicol, cefamandol, chloramphenicol, clavulanic acid, clindamycin, comptothecin, demeclocyclin, doxycyclin, imipenem, latamoxef, novobiocin, oleandomycin, oxytetracyclin, tetracyclin and thiamenicol;
prostaglandins such as arbaprostil, carboprost and prostacydin;
antidepressives such as 8-hydroxychlorimipramine and 2-hydroxyimipramine;
antihypertonics such as sotarol and fenoldopam;
anticholinerogenics such as biperidine, carbidopa, procyclidin and trihexyphenidal;
antiallergenics such as cromolyn;
glucocorticoids such as betamethasone, budenosid, chlorprednison, clobetasol, clobetasone, corticosteron, cortisone, cortodexon, dexamethason, flucortolon, fludrocortisone, flumethasone, flunisolid, fluprednisolon, flurandrenolide, flurandrenolon acetonide, hydrocortisone, meprednisone, methylpresnisolon, paramethasone, prednisolon, prednisol, triamcinolon and triamcinolon acetonide;
narcotic agonists and antagonists such as apomorphine, buprenorphine, butorphanol, codein, cyclazocin, hydromorphon, ketobemidon, levallorphan, levorphanol, metazocin, morphine, nalbuphin, nalmefen, naloxon, nalorphine, naltrexon, oxycodon, oxymorphon and pentazocin;
stimulants such asmazindol and pseudoephidrine;
anaesthetics such as hydroxydion and propofol;
β-receptor blockers such as acebutolol, albuterol, alprenolol, atenolol, betazolol, bucindolol, cartelolol, celiprolol, cetamolol, labetalol, levobunelol, metoprolol, metipranolol, nadolol, oxyprenolol, pindolol, propanolol and timolol;
α-sympathomimetics such as adrenalin, metaraminol, midodrin, norfenefrin, octapamine, oxedrin, oxilofrin, oximetazolin and phenylefrin;
β-sympathomimetics such as bamethan, clenbuterol, fenoterol, hexoprenalin, isoprenalin, isoxsuprin, orciprenalin, reproterol, salbutamol and terbutalin;
bronchodilators such as carbuterol, dyphillin, etophyllin, fenoterol, pirbuterol, rimiterol and terbutalin;
cardiotonics such as digitoxin, dobutamin, etilefrin and prenalterol;
antimycotics such as amphotericin B, chlorphenesin, nystatin and perimycin;
anticoagulants such as acenocoumarol, dicoumarol, phenprocoumon and warfarin;
vasodilators such as bamethan, dipyrimadol, diprophyllin, isoxsuprin, vincamin and xantinol nicotinate;

antihypocholesteremics such as compactin, eptastatin, mevinolin and simvastatin; miscellaneous drugs such as bromperidol (antipsychotic), dithranol (psoriasis) ergotamine (migraine) ivermectin (antihelminthic), metronidazole and secnizadole (antiprotozoals), nandrolon (anabolic), propafenon and quinadine (antiarythmics), srotonin (neurotransmitter) and silybin (hepatic disturbance).

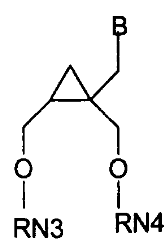
The invention is applicable to L and D- nucleosides bearing di, tri and tetrahydric (that is bearing 2, 3 or 4 hydroxy groups on the (pseudo)saccharide, such as those of the formula N-3:



N-3

where B is a natural or unnatural nucleotide base,
R_{N1} is O or $-CH_2-$, S
R_{N2} and R_{N3} are each H or R_{N2} is methylene or -CH(OH)- and R_{N5} is a bond thereto, or R_{N2} and R_{N5} together are a bond;
n is 0 or 1;
one of R_{N3} and R_{N4} comprises a linker-R_2 structure such as those of formulae IIaa, II'aa, IIc', IIe', IIf*, id' and the other is hydrogen or a further linker-R_2 structure.

An alternative group drugs to which the invention is applicable includes those of formula N-3a:

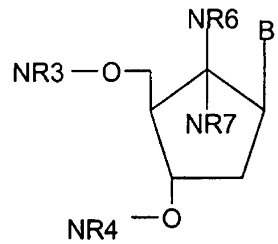


N-3a

where B, NR3 and NR4 are as defined above.

Preferably the linker$(R_2')_k$-R_2 structure is esterified to R_3 in the above two structures, that is the nominal 5' hydroxy group of the nucleoside analogue.

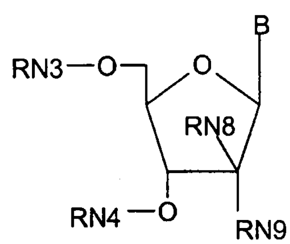
An alternative group of drugs within the scope of the invention has the formula N-3b:



N-3b

where B, RN3and RN4 are as defined above and RN6 is fluoro and RN7 is hydrogen or RN6 and RN7 are both fluoro or RN6 and RN7 together define an exo-methenyl group. The preferred base is guanine in this alternative.

A further group of nucleosides within the scope of the invention has the formula N-3c



N-3c

where B, RN3 and RN4 are as defined above, RN8 and RN9 are fluoro (or one of them is fluoro and the other is hydrogen) or RN8 and RN9 together define exomethenyl or exomethenyl mono or di-subsituted with fluoro. These nucleosides have anticancer activity.

The invention is also applicable to other nucleosides having at least two hydroxy groups, but outside the scope of formula N-3a-c, for instance, 9-[3,3-dihydroxymethyl-4-hydroxy-but-1-yl]guanine as described in WO 95/22330 and 9-

[4-hydroxy-(2-hydroxymethyl)butyl]guanine as described in EP 343 133. The invention is applicable to both L and D stereo forms of the various nucleoside analogues

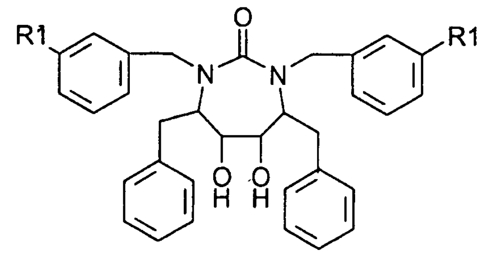
The compounds of the invention, especially cytosine or guanine derivatives where NR1 is oxygen, n is 1 and NR2 and NR5 define a ring are also active against certain retroviral infections, notably SIV, HIV-1 and HIV-2, and Hepatitis B virus. The compounds of the invention, especially cytosine, guanosine or 6-methoxyguanosine derivatives wherein NR1 is oxygen, n is 0 and NR2 and NR5 define an arabinose ring are potent anticancer compounds.

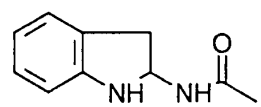
The compounds of the invention, especially derivatives comprising a 1,2,4-triazole-3-carboxamide base, where NR1 is O, NR2 is -CH(OH)-, NR3 is a bond thereto and n is 0 (ribavirin) are expected to be active against hepatitis C virus (HCV). Compounds comprising a substituted benzimidazole base, where NR1 is O, NR2 is -CH(OH)-, NR5 is a bond thereto and n is 0 (for instance Glaxo Wellcome's 1263W94 where the base is 2-isopropylamin-5,6-dichloro-benzimidazol-3-yl) are expected to be active against CMV. Compounds comprising an adenine base, where NR1 is O, NR2 is -CH(OH)-, NR5 is a bond thereto and n is 0 (vidarabine) are expected to be active against HSV encephalitis. Compounds comprising a 2-chloroadenine base with a 2'-deoxyribose sugar are expected to have anticancer activity.

The nucleoside derivatives of the invention are particularly useful for guanine nucleoside and analogues which tend to have poorer uptake than pyrimidine nucleosides. Accordingly B is preferably guanine or a guanine derivative.

A group of hydroxy bearing drugs which are particularly amenable to the prodrugs of the invention are the ring hydroxy compounds. By ring hydroxy is meant that the hydroxy function to which the prodrug of the invention is bound is bonded directly onto an aromatic or non-aromatic, heterocyclic or carbocyclic ring structure.

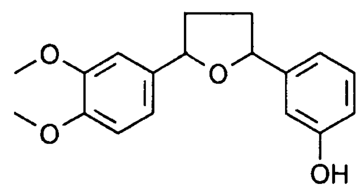
Examples of ring hydroxy compounds include the cyclic urea HIV protease inhibitors, such as those described in WO 9843969, WO9820008, and WO 9419329. Representative protease inhibitors include:



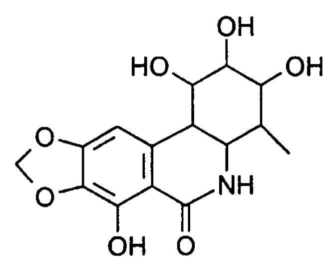
where R1 is NH_2 (DMP 450) or 

(SD 146).

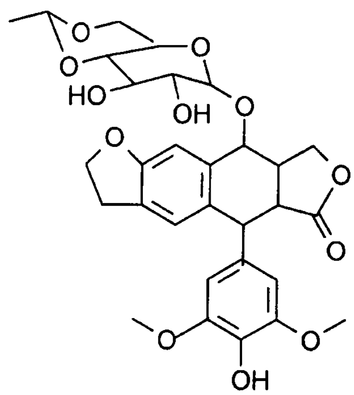
Some examples of phenolic ring hydroxy compounds include the PETT NNRTI discussed below or the compound described in J Med Chem 35 3467 (1992):



Pancratistatin described in Anticancer Drug Design 10: 243 & 299 (1995) and Bioorg Med Chem Lett 6 157 1996:

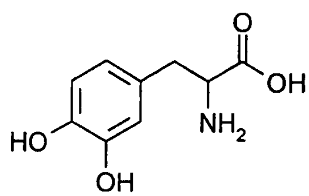


has both phenolic and carbocyclic ring hydroxy functions. A further useful drug with a combination of phenolic and carbocyclic hydroxy functions is etoposide:



as described in Bioorg Med Chem Lett 4 2567 (1994) and Clinical Cancer Res 1 105 1995.

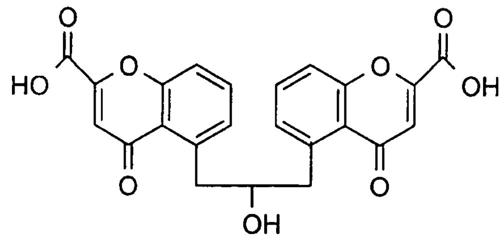
A further convenient Drug for appying the prodrugs of the invention is the anti-Parkinsonian agent levodopa:



This drug has four accessible functions for applying the prodrugs of the invention, namely the 3 and 4 hydroxy groups on the phenyl and the amino and carboxy functions on the side chain.

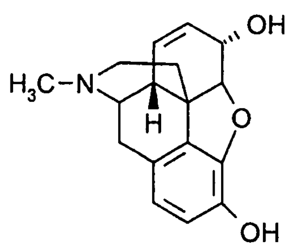
A structure of the formula IIa or II"b can be esterified to one or both of the aromatic hydroxyl functions or amide-bonded to the levodopa amino function. A trifunctional linker of Formula III or Formula IId, can be carbonyl bonded to the levodopa carboxyl function. Such "blocked" carboxyl levodopa compounds are conceivably less susceptible to in vivo peripheral decarboxylation than levodopa and may thus allow the diminution or omission of the customarily coadministered decarboxylase inhibitors such as carbidopa.

A further convenient Drug for applying the prodrugs of the invention is chromoglycate, also known as cromolyn, useful in the treatment of asthma, allergic rhinitis, mastocytosis, ulcerative colitis and inflammatory bowel disease:



It will be apparent that cromolyn has three accessible functions suitable for applying the prodrugs of the invention. In particular, a linker of the formula IId can be carbonyl linked to either of the carboxy groups. As cromolyn is a symmetric compound it may be advantageous to bond a respective linker to each of the carboxyl groups. Alternatively or additionally, a linker of the formula IIa, IId, such as those wherein T is a bond or -O- and V is a bond can be esterified to the hydroxy group depending from the propylene bridge, optionally in conjunction with conventional pharmaceutical esters on the carboxy groups.

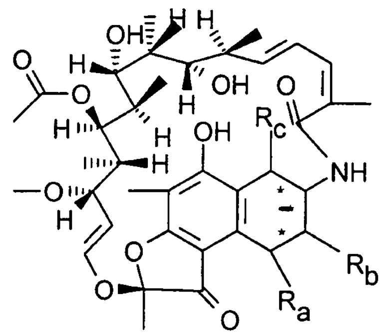
A further group of Drugs which are amenable to the prodrugs of the invention are the pain-killer opiates such as morphine:



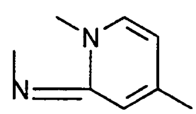
Morphine and many of its analogues have a pair of hydroxy functions accessible to the prodrug approach of the invention. For instance a structure of formula IIa wherein T is a bond or -O- and V is a bond would be convenient for esterification with the 3 and/or 6 hydroxy groups.

A further convenient group of compounds include the macrolide antibiotics such as erythromycin and roxitromycin and antibacterial glycopeptides such as vancomycin.

A further convenient group of Drugs for applying the prodrugs of the invention are the rifamycin antibiotics:

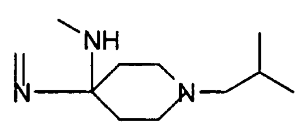


wherein the asterisks define the requisite number of aromatic bonds, including rifampicin (R_a is OH, R_b is -CH=N-(4-N-methylpiperazine), R_c is hydroxy), rifamide (R_a is $OCH_2CONH(C_2H_5)_2$, R_b is hydrogen, R_c is hydroxy), rifamycin B (R_a is $-OCH_2COOH$, R_b is hydrogen, R_c is hydroxy), rifamycin O (R_a is -1,3-dioxolan-4-on)-2-yl, R_b is hydrogen, R_c is hydroxy), rifamycin S (R_a is =O, R_b is hydrogen, R_c is =O), rifamycin SV (R_a is -OH, R_b is hydrogen R_c is -OH), rifaximin (R_a and R_b together define a structure:



, R_c is hydroxy), and

rifabutinum (R_a and R_b together define a structure:

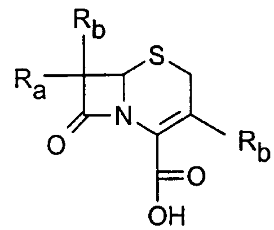


, R_c is =O).

It will be apparent that the rifamycins have a number of free hydroxyls and secondary amines available for esterification or amide bonding with respective linker-R_2 groups

in accordance with the invention such as those of Formula IIa above, which linker group is bonded to one of said hydroxy or amino groups.

A further group of Drugs which are amenable to the prodrugs of the invention is the cephalosporin antibiotics:



Representative cephalosporins include:

cefpodoxime (R_a is [(2-amino-4-thiazolyl)(methoximino)acetyl]amino-, R_b is H, R_c is ethyl),

cefaclor (R_a is aminophenylacetylamino, R_b is H, R_c is chloro),

cefadroxil (R_a is [amino-(4-hydroxyphenyl)acetyl]amino, R_b is H, R_c is methyl);

cefamandole (R_a is [amino-(4-hydroxyphenyl)acetyl]amino, R_b is H, R_c is [1-methyl-1H-tetrazol-5-yl)thio]methyl);

cefatrizine, (R_a is is [amino-(4-hydroxyphenyl)acetyl]amino, R_b is H, R_c is [1H-1,2,3-triazol-4-ylthio]methyl);

cefazedone (Ra is [(3,5-dichloro-4-oxo-1(4H)-pyridinyl)acetyl]amino, R_b is H, R_c is [(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl),

cefazolin (Ra is (1H-tetrazol-1-ylacetyl)-amino Rb is H, Rc is [(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl,

cefbuparazone (Ra is [2-[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]-3-hydroxy-1-oxobutyl]amino, Rb is OCH_3, Rc is [(1-methyl-1H-tetrazoly-5yl)thio]methyl,

cefixime (Ra is [(2-amino-4-thiozolyl)[carboxymethoxy)imino]acetyl]amino, Rb is H, Rc is -CH=CH_2),

cefmonoxime, (Ra is [(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino, Rb is h, rc is [(1-methyl-1H-tetrazol-5-yl)thio]methyl),

cefmetazole ([[(cyanomethyl)thio]acetyl]amino, Rb is H, Rc is [1-methyl-1H-tetrazol-5-yl)thio]methyl),

cefminox (Ra is [[(2-amino-2-carboxyethyl)thio]acetyl]amino, Rb is OCH_3, Rc is is [1-methyl-1H-tetrazol-5-yl)thio]methyl),

cefodoxime (Ra is [(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino, Rb is H, Rc is [[5-(carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl),

cefonicid (Ra is (hydroxyphenylacetyl)amino, Rb is H, Rc is [[1-8sulfomethyl)-1H-tetrazol-5-y]thio]methyl),

cefoperazone (Ra is [[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino, Rb is H, Rc is [(1-methyl-1H-tetrazol-5-yl)thio]methyl),

ceforanide (Ra is [[2-(aminomethyl)phenyl]acetyl]amino, Rb is H, Rc is [[1-(carboxymethyl)-1H-tetrazol-5-yl]thio]methyl),

cefotaxime (Ra is [(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino, Rb is H, Rc is (acetyloxy)methyl),

cefotetan (Ra is [[4-(2-amino-1-carboxy-2-oxoethylidine)-1,3-dithietan-2-yl]carbonyl]amino, Rb is OCH_3, Rc is [(1-methyl-1H-tetrazol-5-yl)thio]methyl, Rc is [(1-methyl-1H-tetrazol-5-yl)thio]methyl),

cefotiam (Ra is [(2-amino-4-thiazolyl)acetyl]amino, Rb is H, Rc is [[1-[2-(dimethylamino)ethyl]-1H-tetrazol-5-yl]thio]methyl),

cefoxitin (Ra is (2-thienylacetyl)amino, Rb is OCH_3, Rc is [aminocarbonyl)oxy]methyl),

cefpimizole (Ra is [[[(5-carboxy-1H-imidazol-4-yl)carbonyl]amino]phenylacetyl]amino, Rb is H, Rc is (4'-(2-sulfoethyl)pyridinium) methyl hydroxide inner salt,

cefpiramide (Ra is [[[(4-hydroxy-6-methyl-3-pyridinyl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino, Rb is H, Rc is [(1-methyl-1H-tetrazol-5-yl)thio]methyl),

cefroxadine (Ra is (amino-1,4-cyclohexadien-1-yl-acetyl)amino, Rb is H, Rc is OCH_3),

cefsulodin (Ra is (phenylsulfoacetyl)amino, Rb is H, Rc is (4'-carbamoyl pyridinium)methyl hydroxide inner salt),

ceftazidime (Ra is [(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino, Rb is H, Rc is pyridiniummethyl hydrochloride inner salt),

cefteram (Ra is [(2-amino-4-thiazolyl)methoxyimino)acetyl]amino, Rb is H, Rc is (5-methyl-2H-tetrazol-2-yl)methyl),

ceftezole (Ra is (1H-tetrazol-1-ylacetyl)amino, Rb is (1,3,4-thiadiazol-2-ylthio)methyl),

ceftibuten (Ra is [2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino, Rb is H, Rc is H)

ceftiofur (Ra is [(2-amino-4-thiazoyl)(methoxyimino)acetyl]amino, Rb is H, Rc is [(2-furanylcarbonyl)thio]methyl),

ceftizoxime (Ra is [(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino, Rb is H, Rc is H),

ceftriaxone (Ra is [(2-amino-4-thiazolyl)methoxyimino)acetyl]amino, Rb is H, Rc is [1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl),

cefuroxime (Ra is [2-furanyl(methoxyimino)acetyl]amino, Rb is H, Rc is [(aminocarbonyl)oxy]methyl),

cefuzonam (Ra is [(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino, Rb is H, Rc is (1,2,3-thiadiazol-5-ylthio)methyl),

cephacetrile (Ra is (cyanocetyl)amino, Rb is H, Rc is (acetyloxy)methyl),

cephalexin (Ra is (aminophenylacetyl)amino, Rb is H, Rc is methyl),

cephaloglycin (Ra is (aminophenylacetyl)amino, Rb is H, Rc is (acetyloxy)methyl),

cephaloridine (Ra is (2-thienylacetyl)amino, Rb is H, Rc is pyridinium methyl hydroxide inner salt),

cephalosporin C (Ra is (5-amino-5-carboxy-1-oxopentyl)amino, Rb is H, Rc is (acetyloxy)methyl),

cephalothin (Ra is (2-thienylacetyl)amino, Rb is H, Rc is (acetyloxy)methyl),

cephamycin A (Ra is (5-amino-5-carboxy-1-oxopentyl)amino, Rb is OCH_3 Rc is $-CH_2OCOC(OCH_3)=CH$-(4-oxysulphyl)phenyl),

cephamycin B (Ra is (5-amino-5-carboxy-1-oxopentyl)amino, Rb is OCH_3 Rc is $-CH_2OCOCC(OCH_3)=CH$-(4-hydroxy)phenyl),

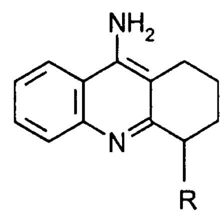
cephamycin C (Ra is (5-amino-5-carboxy-1-oxopentyl)amino, Rb is OCH_3 Rc is $-CH_2OCONH_2$)

cephapirin (Ra is [(4-pyridinylthio)acetyl]amino, Rb is H, Rc is (acetyloxy)methyl),

cephradine (Ra is (amino-1,4-cyclohexadien-1-yl-acetyl)amino, Rb is H, Rc is CH_3).

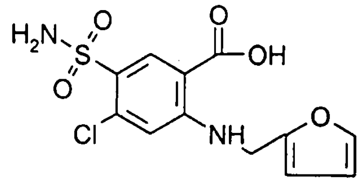
Common for the above cephalosporins is the presence of a carboxy group at the 2-position which is amenable to derivation with a linker group, in particular those of the Formula IId defined above. The above listed Ra, Rb and Rc groups may also be combined in various permutations and the invention includes prodrugs of all such cephalosporins.

A further group of Drugs which are amenable to the prodrugs of the invention are the anticholinesterases such as tacrine:



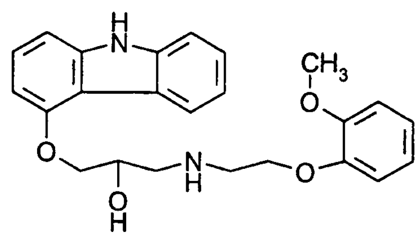
where R is H or OH. It will be apparent that the tacrine itself (R=H) has a free amine group suitable for derivatisation with a linker-R_2 group such as those of Formula IIa, for instance when T is a bond or -O- and V is a bond. The tacrine metabolite (R = OH), which is also active in vivo has an additional hydroxy function which can alternatively or additionally be derivatised with a linker such as those of Formula IIa, for instance when T is a bond or -O- and V is a bond.

A further group of Drugs which are amenable to the prodrugs of the invention are the sulphonamide diuretics such as furosemide:



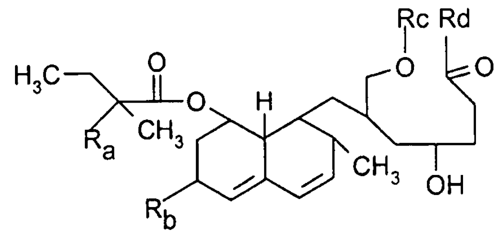
It will be apparent that furosemide has a free carboxylic function, a primary amine and a secondary amine amenable to the prodrugs of the invention. In particular an R_2 bearing linker, such as those of Formula III, or Formula IId can be carbonyl linked to the free carboxy function. Alternatively or additionally, an R_2 bearing linker, such as those of Formula IIa, for instance where T is a bond or -O- and V is a bond can be amide bonded to the primary and/or secondary amine groups.

A further group of Drugs amenable to the prodrugs of the invention include the α-1 and β-blocker carvedilol compounds:



Carvedilol has a free hydroxy function, a secondary heterocyclic amine and a further secondary amine on the side chain, which are amenable to the prodrugs of the invention, such as those of Formula II'a, for instance where T is a bond or -O- and V is a bond which is in turn linked to the hydroxy and/or the ring amine and/or the side chain amine functions on carvedilol.

A further group of Drugs which are amenable to the prodrugs of the invention are the hypolipaemic statins, such as flustatin or compounds of the formula:



such as pravastatin (Ra = H, Rb = OH, Rc = H , Rd = OH) and simvastatin (Ra = CH_3, Rb = CH_3, Rc and Rd together define a bond).

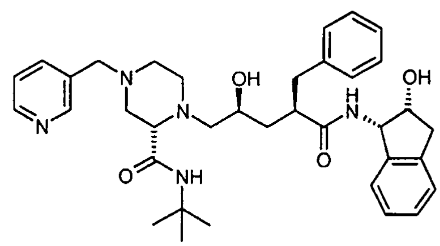
Taking simvastatin as an example, it will be apparent that there is a free side chain hydroxyl which is available for linkage with an R_2 bearing linker, such as those of Formula IIa, for instance where T is a bond or -O- and V is a bond.

The statin pravastatin also bears a corresponding hydroxy function and can be derivatised with a linker in the same fashion. Pravastatin also bears a ring hydroxyl and a further side chain hydroxyl function which can be derivatised with a linker in a corresponding fashion. Pravastatin also bears a carboxyl function which can additionally or alternatively be derivatised with an R_2 bearing linker such as those of Formula III, or Formula IId.

A further group of Drugs which are amenable to the prodrugs of the invention are peptides and pseudopeptides such protease inhibitors including antifibrinolytics like aprotinin or peptidomimetic aspartyl protease inhibitors such as renin inhibitors. Other peptide Drugs include hormones such as vasopressins. Taking vasopressins as an example, peptide Drugs may be cyclic oligopeptides consisting solely of amino acids such as desmopressin or oxytocin, wherein the N and C terminals represent accessible functions for derivatisation in accordance with the invention. Additionally many peptide drugs include amino acids with side chains bearing accessible functions such as arginine, serine or aspartate. Alternatively a peptide Drug, particularly peptidomimetics can be derivatised with non-amino acid structures bearing accessible functions such as somatostatin octreotide.

Useful oligopeptides for derivisation according to the invention include MK 383, an Arg-Gly-Asp analogue useful as an antithrombotic, DADLE (Tyr-D-Ala-Gly-Phe-D-Leu), an encephalin analogue and NISIN.

An exemplary group of protease inhibitors amenable to the invention comprises the HIV protease inhibitors bearing one or more chain hydroxy functions and/or one or more ring hydroxy functions such as the indanolamine terminal group in Mercks indinavir:



Favoured prodrugs of indinavir in accordance with the invention include

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(3-valyloxypropionyloxy)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(3-isoleucyloxypropionyloxy)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(4-valyloxybutyryloxy)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(4-isoleucyloxybutyryloxy)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(4-valyloxybut-2-en-oyl)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(4-isoleucyloxybut-2-enoyloxy)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(5-valyloxypent-2-en-oyl)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(5-isoleucyloxypent-2-enoyloxy)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

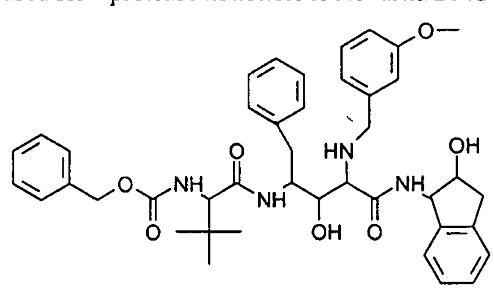
[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(5-valyloxypent-3-en-oyl)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(5-isoleucyloxypent-3-enoyloxy)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(2-valyloxypropionyloxy)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide,

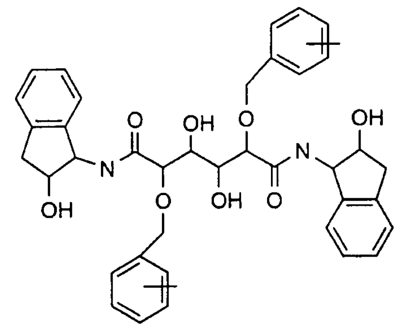
[1-(1S,2R), 5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-(2-isoleucyloxypropionyloxy)-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-D-erythro-pentonamide, and the like.

A further indanol based HIV protease inhibitors is Novartis/BMS SDZ PRI 053:

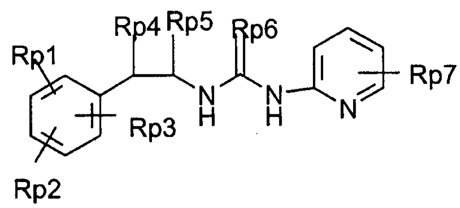


Favoured compounds include the analogues listed as for indinavir,

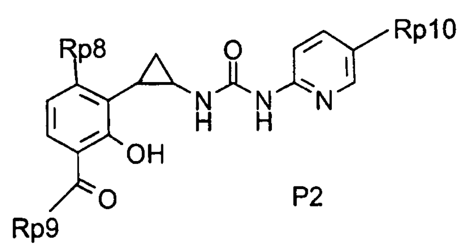
A further group of HIV protease inhibitors include the hexose derived compounds described in WO 98/45330, such as:



A further useful group of compounds for applying the compounds of the invention are the phenolic hydroxy compounds of the PETT series of NNRTI disclosed in WO 93/03022, WO95/06034 and PCT/SE99/00053, the contents of which are incorporated by reference. Favoured ring hydroxy compounds of this class have the formula P1:



where one of Rp1-3 is hydroxy and the others are hydrogen, halo, C_{1-6} alkanoyl, C_{1-6} alkyl, C_{1-6} alkoxy etc as defined in WO95/06034, Rp4 and Rp5 are hydrogen or join to form a cis-cyclopropyl or cyclobutyl group, Rp6 is O or S and Rp7 is halo, cyano, amino etc as defined in WO95/06034. Particularly preferred compounds of this class have the formula P2:



P2

wherein

Rp8 is halo;

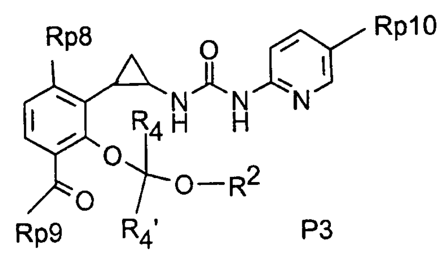
Rp9 is C_1-C_3 alkyl;

Rp10 is halo, especially bromo or cyano

The phenolic hydroxy function is bonded to any of the generic structures above, such as those depicted in formula IIa, IIb, IIc, IId, IIe, IIf, Id, etc. These compounds are prepared by acylation of the relevant mother compound of formula P-1 or P-2 with the activated structure IIa, IIb etc, wherein the or each R_2 group is conventionally N-protected, followed by deprotection.

As the compounds of formula P2 include an electron withdrawing group on the phenol ring to which the prodrug moiety is attached it is generally preferred to avoid direct esters such as 4-valyloxybutyric acid derivatives which are otherwise effective on phenols and carbocyclic ring hydroxy functions.

Using these NNRTIs as an example of a phenolic hydroxy, a convenient group of prodrugs have the formula:

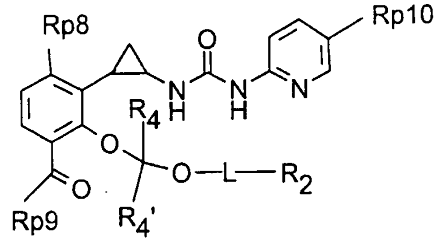


P3

wherein

Rp8, Rp9, Rp10, R^2, R_4 and R_4' are as defined above. Typically both of R_4 and $R_{4'}$ are H.

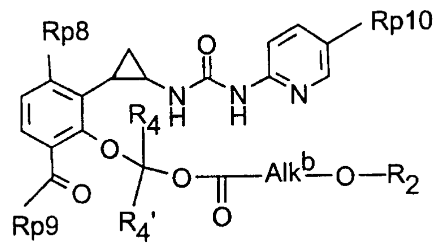
An alternative preferred group of phenolic prodrugs of the invention have the Formula P4:



P4

where Rp8, Rp9, Rp10, R_4 and $R_{4'}$ are as defined above. L and R_2 define a linker group and residue of an aliphatic amino acid, such as those of Formulae IIa, IIb, IIc, IId, IIe, IIf or those depicted in Formulae Ia and Id. Typically both of R_4 and $R_{4'}$ are H.

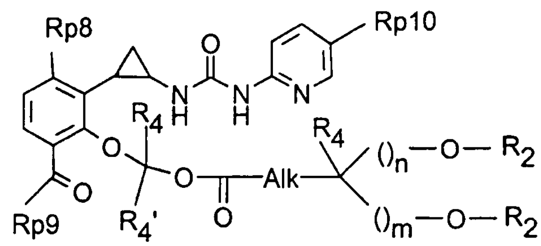
Favoured compounds within the class described in the immediately preceding paragraph include those of the formula P5:



P5

where Rp8 Rp9, Rp10, R_4, $R_{4'}$ and R_2 are as defined above and Alk^b is C_1-C_6 optionally branched, optionally monounsaturated alkyl.

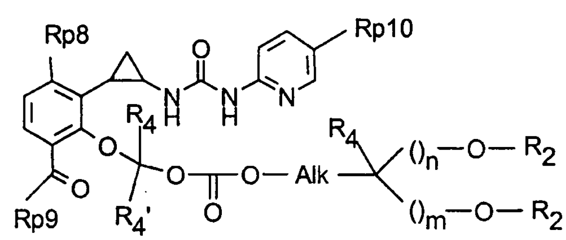
One variant of a branched Alk^b in Formula P5 can be substituted with hydroxy which in turn is esterified with a further R^2, thus defining a linker of the formula IIa, as depicted in Formula P6:



P6

where Rp8, Rp9, Rp10, Alk, R_4, R_4', m, n and R_2 are as defined above. Preferably each occurrence of Rx and Rx' is H. Particularly favoured values for Alk, m and n include: methylene:1:1 and absent: 1:0 respectively.

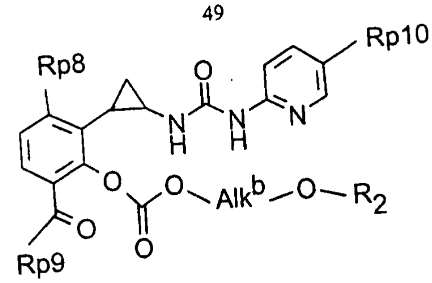
A further favoured group of compounds has the Formula P7:



P7

where Rp8, Rp9, Rp10, Alk, R_4, R_4', m, n and R_2 are as defined above or wherein the -$()_m$-O-R_2 arm is absent. Preferably each occurrence of Rx and Rx' is H. Particularly favoured values for Alk, m and n include:absent:1:1, thus defining a glycerol derivative, wherein or -$()_m$-O-R_2 ar is absent and Alk and n are absent:1 with R_4, R_4 and R_4' as H.

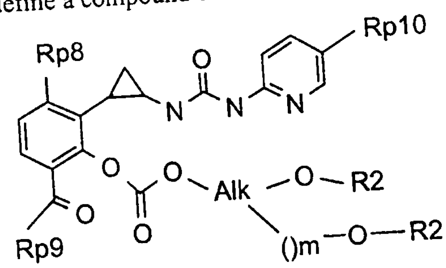
A further favoured group of phenolic hydroxy compounds omit the methyloxy group immediately adjacent the phenolic hydroxy function:



P8

where Rp8, Rp9, Rp10, R_2, and Alk^b are as defined above. Currently favoured values for Alk include methylene, ethylene, 1,1-dimethylethylene, propylene, butylene and, in the case of said $-OR_2$ substitution, glycerol.

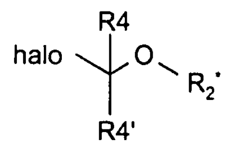
As with Formula P5/P6 and P7/P7', Alk^b in formula P8 can comprise an additional $-O-R_2$ substitution to define a compound of the formula P8'



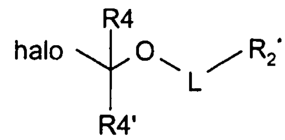
P8'

where each of the variables is as defined above.

It will be appreciated that the NNRTI mother compound in formulae P-3-8' has been shown as an example of a phenolic hydroxy and that the respective prodrug moiety will be applicable to otther ring hydroxy functions of a drug, particularly those subject to electron withdrawing effects. Compounds of this phenolic hydroxy aspect of the invention are typically prepared by alkylation of the corresponding mother compounds. In particular, the preparation of compounds of formula P-3 or P-4 generally proceeds by alkylation using conventional coupling conditions of the mother compound with the corresponding intermediate:

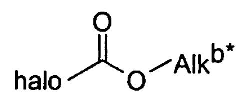


or



where Rx and L are as defined above and R_2* is R_2 as defined, but N-protected with a conventional N-protecting group. Preferably the halogen activating group is iodo, which is in turn prepared by iodination of the corresponding chloro analogue. Typical coupling conditions include treatment with a base in an organic solvent such as THF prior to addition of the halogenated intermediate followed by conventional deprotection of the R_2 N-protecting group.

Compounds of formula P-8 are generally prepared by esterification of a compound of the formula P-2 with an intermediate of the formula:



where Alk^{b*} is a functionalised Alk^b as described above, for example chloromethyl chloroformate, in an organic solvent, followed by iodination of the terminal chloro with NaI (or other activation of the functionalising group) and reaction with an N-protected R_2.

It will be apparent that many linker (R_2')-R_2) groups, particularly trifunctional linkers or those wherein R_4 and R_4' differ will define chiral structures and the phamraceutical compounds or intermediates of the invention include all enantiomers thereof, as racemates or as preparations of > 80%, preferably > 95% enantiomerically pure compound.

The compounds of the invention can form salts which form an additional aspect of the invention. Appropriate pharmaceutically acceptable salts of the compounds of Formula I include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, isethionate, adipate, alginate, aspartate, benzoate, butyrate,

digluconate, cyclopentanate, glucoheptanate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, proprionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-napthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, phosphoric and sulphonic acids. The compounds of Formula I may in some cases be isolated as the hydrate.

The pharmaceutical compounds of the invention are generally prepared by alkylation or acylation of the respective mother compounds. Alkylation or acylation generally proceeds via an activated derivative. The activated derivative used in an acylation may comprise e.g, the acid halide, acid anhydride, activated acid ester or the acid in the presence of coupling reagent, for example dicyclohexylcarbodiimide, where "acid" to a precursor group such as those of the formula PGNHC(R_d)COO-Lα-COOH, where R_d is defined above, PG is a conventional N-protecting group and L_α is the residue of the linker.

The activated derivative used in the acylation may comprise e.g, the acid halide, acid anhydride, activated acid ester or the acid in the presence of coupling reagent, for example dicyclohexylcarbodiimide. Representative activated acid derivatives include the acid chloride, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinamide derived esters, N-hydroxyphthalimide derived esters, N-hydroxy-5-norbornene- 2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like. Further activated acids include those where X in the formula RX represents an OR'moiety where R is linker$(R_2)_k$-R_2 or R_2 as defined herein, and R' is, for example $COCH_3$, $COCH_2CH_3$ or $COCF_3$ or where X is benzotriazole.

Activated L-R_y groups wherein L is derived from an hydroxyalkanoic acid are conveniently prepared by esterification of conventionally carboxy protected hydroxyalkanoic acid, such as glycollic acid or lactic acid or more preferably

an ω-hydroxyalkanoic acid such as 3-hydroxypropionic acid, 4-hydroxybutyric acid, 5-hydroxypentanoic acid etc with the appropriate N-protected R_y derivative, such as N-Cbz-isoleucine, either as the free acid in conjunction with a coupling agent such as DCC, or activated, for instance to the corresponding acid halide. The carboxy protecting group is removed as is known in the art and the resulting intermediate activated and esterified with the mother compound with the methodology described above. The N-protecting group on R_y is then removed by conventional deprotection conditions.

Activated L-R_y groups wherein L is derived from a cis-alkenoic acid, such as 4-hydroxy-cis-but-2-en are conveniently prepared from the corresponding haloalkanoic acids, such as 4-bromo-cis-but-2-enoic acid which is carboxy protected, for instance with t-butyl prior to conventional esterification under with the appropriately N-protected R_y moiety, sicha N-Cbz-valine. The carboxy protecting group is removed and the free carboxy activated and esterified with the mother compound as described above, followed by deprotection of the N-protecting group.

Activated L-R_y groups wherein L is derived from a 2-hydroxymethylbenzoic acid can be prepared from 2-methylbenzoic acid which is carboxy protected and brominated by conventional techniques. This activated intermediate is esterified with an appropriately N-protected R_y moiety, such as Cbz-valine. This intermediate is carboxy deprotected and esterified with the mother compound as described above, followed by deprotection of the R_y N-protecting group.

The reactive derivatives of the X-linker(N-PG-R_2')-N-PG-R_2 intermediates implied above may be pre-formed or generated in situ by the use of reagents such as dicyclohexylcarbodiimide (DCC) or O-(1H-benzotriazol-1-yl) N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU). When an acid halide, such as the acid chloride is used, a tertiary amine catalyst, such as triethylamine, N,N'-dimethylaniline, pyridine or dimethylaminopyridine may be added to the reaction mixture to bind the liberated hydrohalic acid.

The reactions are preferably carried out in an unreactive solvent such as N,N-dimethylformamide, tetrahydrofuran, dioxane, acetonitrile or a halogenatated hydrocarbon, such as dichloromethane. If desired, any of the above mentioned tertiary amine catalysts may be used as solvent, taking care that a suitable excess is present. The reaction temperature can typically be varied between 0° C and 60° C, but will preferably be kept between 5° and 50° C. After a period of 1 to 60 hours the reaction will usually be essentially complete. The progress of the reaction can be followed using thin layer chromatography (TLC) and appropriate solvent systems. In general, when the reaction is completed as determined by TLC, the product is extracted with an organic solvent and purified by chromatography and/or recrystallisation from an appropriate solvent system.

By-products where acylation has taken place on inappropriate places on the Drug can be separated by chromatography, but such misacylation can be minimized by controlled reaction conditions. These controlled conditions can be achieved, for example, by manipulating the reagent concentrations or rate of addition, especially of the acylating agent, by lowering the temperature or by the choice of solvent. The reaction can be followed by TLC to monitor the controlled conditions..

Linkers of Formula IIa may alternatively be amide bonded to free primary or secondary amine functions on the Drug using conventional chemistry in the peptide art.

Linkers of Formula IIIa or IVd or the corresponding derivatives of Formula III' and II'd will generally be acylated to free carboxyl functions on the Drug in an analogous, but reversed fashion to the above described acylation of Drugs with hydroxy functions. US 4 486 425 which is incorporated by reference illustrates a convenient process.

Linkers of Formula IVa wherein V comprises a structure of the formula IIcc can be prepared by a by a two stage process. In particular a compound of the formula $ClC(=O)OC(R_4)(R_4')Cl$ can be reacted with a suitable accessible hydroxy function on the Drug (optionally protected on other functions with conventional protecting groups) as is known in the cephalosporin art. The resulting Drug-O-$C(=O)OC(R_4)(R_4')$chloride is then reacted with an R_2 bearing linker wherein a free function comprises a carboxyl function, such as the potassium salt.

Intermediates of the formula IId are conveniently prepared by acylation of a carboxy-protected hydroxy alkanoic acid, typically a 2-hydroxy-1-alkanoic acid, with the appropriate activated and N-protected R_2 derivative, such as N-CBZ valyl or isoleucyl in conjunction with a conventional coupling reagent such as DMAP/DCC or with the amino acid halide. The carboxy protecting group is then removed, for instance by acid hydrolysis and the resulting intermediate is activated as described above or the free acid is unsed in conjunction with a coupling reagent to esterify the the nucleoside under conventional esterification conditions.

Compounds within the scope of the invention are also conveniently prepared by the methodology in the immediately preceding paragraph, namely esterification of a carboxy protected α- hydroxy, ω-carboxy acid, such as glycollic acid, lactic acid, hydroxybutyric acid etc with the appropriate N-protected R_2 derivative, either as the free acid in conjunction with a coupling agent or activated, for instance to the corresponding acid halide. The carboxy protecting group is removed and the resulting intermediate esterified with the nucleoside with the methodology described above.

Compounds comprising a structure of the formula IIe or IIf are prepared by carboxy protecting the terminal carboxy groups of the respective dicarboxylic acid, such as L-tartaric acid or L-malic acid, with conventional carboxy protecting groups such as benzyl. The free hydroxy group (s) are then esterified with conventional esterification techniques, such as DMAP & DCC in DMF with the appropriate N-protected R_2 amino acid, such as N-Boc-L-valyl or N-Boc-L-isoleucyl. The benzyl carboxy protecting groups are removed and the resulting product is esterified to the 5'-

hydroxy function of a monohydric nucleoside, using conventional conditions, such as those in the accompanying Examples. Finally, the free carboxy function is esterified with an R_1 group or, more preferbably a conventional pharmaceutically acceptable ester, such as the ethyl ester.

Trifunctional of formula IIa wherein and n and m are 1 and Alk is absent can be prepared from glycerol by regioselective esterification as described in PCT/SE98/01467. In short R_2 and R_2' are regioselectively esterified to positions 1 and 3 of the glycerol and position 2 is then converted to the appropriate -T-C(=O)- group, which is then esterified to an accessible function on the Drug, or alternatively to a cooperating function on an intermediate linker, such as succinic acid which is in turn linked to the accessible funciton on the Drug. Glycerol based linkers where T comprises an -NH- group can be prepared by analogous regioselective esterification followed by conversion of the free hydroxyl to amine, reduction to azide and reaction with phosgene to form the corresponding chlorocarbamate.

Linkers where m and n are 1, Alk is alkylene or alkenylene and T is a bond can be prepared analagously to the methodology in PCT/SE98/01467. Other permutations of m, n, Alk and the various functions in the trifunctional linker group L_1 of formula IIa can be prepared analagously to the above with the corresponding starter materials, such as 1,2,4-trihydroxybutane (CA registry number 3968-00-6), 3,4-dihydroxybutanoic acid (1518-61-2 & 22329-74-4), (S)-3,4-dihydroxybutanoic acid (51267-44-8), (R)-3,4-dihydroxybutanoic acid (158800-76-1), 1,2,5-pentanetriol (51064-73-4 & 14697-46-2), (S)-1,2,5-pentanetriol (13942-73-9), (R)-1,2,5-pentanetriol (171335-70-9), 4,5-dihydroxypentanoic acid (66679-29-6 & 129725-14-0), 1,3,5-pentanetriol (4328-94-3) and 3-(2-hydroxyethyl)-1,5-pentanediol (53378-75-9). The preparation of each of these starting materials is described in the references to the respective registry number. Ohsawa et al in Chem Pharm Bull 41 (11) 1906-1909 (1993) and Terao et al Chem. Pharm. Bull. 39(3) 823-825 (1991) describe the control of the sterochemistry of trifunctional linker groups with lipase P.

Pharmaceutical compounds in accordance with the invention may also be prepared in a step wise manner, for instance a compound of the formula ClC(=O)OC(R_4)(R_4')Cl

or can be reacted with an hydroxy group of the Drug (optionally protected on the other vulnerable functional groups with conventional protecting groups). The resulting drug-O-C(=O)OC(R_4)(R_4')chloride is then reacted with an N-protected-R_2 or a di or tri trifunctional linker bearing an N-protected R_2 in which the third function comprises a carboxyl function.

The amino acid derivative of R_2 and, if present, R_1 can alternatively be esterified to the linker group with the 2-oxa-4-aza-cycloalkane-1,3-dione methodology described in international patent application no. WO 94/29311, the contents of which are hereby incorporated by reference.

Linking of the carboxy function of R_2 to an amine group on the linker derivative proceeds by conventional peptide chemistry, generally in conjunction with protection of the α-amine with conventional N-protecting groups. Formation of an amide bond between a carboxyl function on the linker and the α-amine group of R_2 also proceeds by conventional peptide chemistry, generally in conjunction with protection of the α-carboxy function.

The preparation of further linker groups and their application to Drugs is shown in the following Examples.

As the Drugs envisaged in the use of the present invention are proven pharmaceuticals, the starting materials for preparing the prodrugs of the invention are either available in commerce or are extensively described in the medical literature, including the FDA and other registration files for the respective drugs.

As used herein "Optional substituents" can include hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkanoyl, haloC_1-C_6 alkyl, amino, halo, cyano, azido, oxo, mercapto and nitro, and the like."Ring" as used herein includes atoms including monocyclic rings such as furyl, thienyl, pyranyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl,

imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, and the like or bicyclic rings especially of the above fused to a phenyl ring such as indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzothienyl etc. The carbo or heterocyclic ring may be bonded via a carbon to the remainder of the linker via a hetero atom, typically a nitrogen atom, such as N-piperidyl, N-morpholinyl etc. The symbol () is used in its conventional sense, that is a methylene group.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York, 1981), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoracetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl, and the like, carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butoxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like; alkyl groups such as benzyl, triphenylmethyl,

benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Favoured N-protecting groups include formyl, acetyl, allyl, F-moc, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butoxycarbonyl (BOC) and benzyloxycarbonyl (Cbz).

Hydroxy and/or carboxy protecting groups are also extensively reviewed in Greene ibid and include ethers such as methyl, substituted methyl ethers such as methoxymethyl, methylthiomethyl, benzyloxymethyl, t-butoxymethyl, 2-methoxyethoxymethyl and the like, silyl ethers such as trimethylsilyl (TMS), t-butyldimethylsilyl (TBDMS) tribenzylsilyl, triphenylsilyl, t-butyldiphenylsilyl triisopropyl silyl and the like, substituted ethyl ethers such as 1-ethoxymethyl, 1-methyl-1-methoxyethyl, t-butyl, allyl, benzyl, p-methoxybenzyl, dipehenylmethyl, triphenylmethyl and the like, aralkyl groups such as trityl, and pixyl (9-hydroxy-9-phenylxanthene derivatives, especially the chloride). Ester hydroxy protecting groups include esters such as formate, benzylformate, chloroacetate, methoxyacetate, phenoxyacetate, pivaloate, adamantoate, mesitoate, benzoate and the like. Carbonate hydroxy protecting groups include methyl vinyl, allyl, cinnamyl, benzyl and the like.

While it is possible for the active agent to be administered alone, it is preferable to present it as part of a pharmaceutical formulation. Such a formulation will comprise the above defined active agent together with one or more acceptable carriers/excipients and optionally other therapeutic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

The formulations include those suitable for rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration, but preferably the formulation is an orally administered formulation. The formulations may conveniently be presented in

unit dosage form, e.g. tablets and sustained release capsules, and may be prepared by any methods well known in the art of pharmacy.

Such methods include the step of bringing into association the above defined active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a pharmaceutical compound of the invention or its pharmaceutically acceptable salt in conjunction or association with a pharmaceutically acceptable carrier or vehicle. If the manufacture of pharmaceutical formulations involves intimate mixing of pharmaceutical excipients and the active ingredient in salt form, then it is often preferred to use excipients which are non-basic in nature, i.e. either acidic or neutral.

Formulations for oral administration in the present invention may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion and as a bolus etc.

With regard to compositions for oral administration (e.g. tablets and capsules), the term suitable carrier includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as

magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring or the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

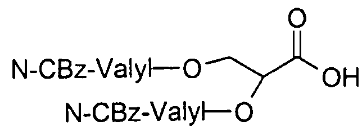
Detailed description

Various aspects of the invention will now be described by way of example only with reference to the following Examples

Preparation of intermediates.

Example AA-I-1

2,3-Bis-(N-CBz-L-valyloxy)-propionic acid.



a) t-Butyl 2,3-bis (N-CBz-L-valyloxy)propionate.

To a solution of t-butyl 2,3-dihydroxypropionate (2.43g, 15 mmole), N-CBz-L-valine (7.54g, 30 mmole) and DMAP (0.37g, 3 mmole) in 150 ml dichloromethane was added DCC (7.2g 35 mmole) and the mixture was stirred for two days at room temperature. The mixture was cooled to about 5°C and the urethane was filtered. The filtrate was evaporated, ethyl acetate was added and the organic phase washed twice with 5% acetic acid, 5% sodium hydrogen carbonate and water. The organic phase was dried with sodium sulfate filtered and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 8.2g = 86%

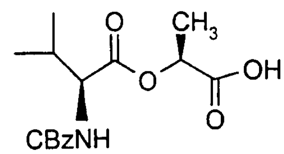
b) 2,3-Bis-(N-CBz-L-valyloxy)-propionic acid.

To a solution of t-butyl -2,3-bis-(N-CBz-L-valyloxy)-propionate (7.2g, 11.4 mmole) in dichloromethane (25 ml) was added trifluoroacetic acid (25 ml) and the solution was stirred for five hours at room temperature. The solution was evaporated under reduced pressure and coevaporated two times with toluene. The product was isolated by silica gel column chromatography. Yield : 5.9g = 90%

^{1}H-NMR (DMSO-d6) 0.92 (m, 12H) 2.08 (m, 2H) 3.92-4.17 (m, 2H) 4.30-4.67 (m, 2H) 5.04 (s, 4H) 5.28 (m, 1H) 7.32 (m, 10H) 7.70 (m, 2H)

Example AA-I-2

(S)-(+)-2-(N-CBz-L-valyloxy)propionic acid



a) 4-Methoxybenzyl (S) (+)-2-hydroxypropionate.

To a stirred solution of (S)(+)2 hydroxypropionic acid (9.0g, 100 mmole) in 100 ml dry DMF was added potassium tert-butoxide (12.34g, 110 mmole) and the mixture was stirred for one hour at 25°C. 4-Methoxybenzyl chloride (18.8g 120 mmole) was added and the mixture was stirred for six hours at 60°C. The mixture was evaporated under reduced pressure and 250 ml ethyl acatate was added. The organic phase was washed four times with water.The organic phase was dried with sodium sulfate and concentrated in vacuo. Yield: 15.6g = 74%

b) 4-Methoxybenzyl (S)-(+)-2-(N-CBz-L-valyloxy)propionate.

To a solution of 4-methoxybenzyl (S)-(+)-2-hydroxypropionate (7.6g, 36 mmole), N-CBZ-L-valine (10.05g, 40 mmole) and DMAP (0.98g, 8 mmole) in 150 ml dichloromethane was added a solution of DCC (8.3g, 40 mmole) and the mixture was stirred overnight at room temperature. The mixture was cooled to about 5°C and the urethane was filtered. The filtrate was evaporated and the product was isolated by silica gel column chromatography. Yield: 14.4g = 90%

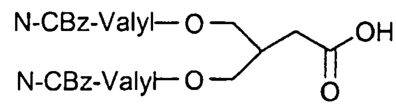
c) (S)-(+)-2-(N-CBz-L-valyloxy)propionic acid.

To a solution of 4-methoxybenzyl (S)-(+)-2-(N-CBz-L-valyloxy)propionate (14.0g, 31.5 mmole) in dichloromethane (50 ml) was added trifluoroacetic acid (25 ml) and the solution was stirred for five hours at room temperature. The solution was evaporated under reduced pressure and coevaporated two times with toluene. The product was isolated by silica gel column chromatography. Yield: 9.4g = 92%

^{1}H-NMR (DMSO-d6) 0.94 (m, 6H) 1.46 (d, 3H) 2.12 (m, 1H) 4.05 (m, 1H) 4.92 (m, 1H) 5.06 (s, 2H) 7.34 (m, 5H) 7.68 (d, 1H)

Example AA-I-3

3,3-Bis (N-CBz-L-valyloxymethyl)-propionic acid



a) 4,4-bis (N-CBZ-L-valyloxymethyl)-but-1-ene.

To a solution of 2-allyl-1,3-propanediol (2.32g, 20 mmole), N-CBZ-L-valine (10.06g, 40 mmole) and DMAP (0.488g, 4 mmole) in 120ml dichloromethane was added DCC (9.08g, 44 mmole) in portions and the mixture was stirred overnight at room temperature. The mixture was cooled to 5°C and the urethane was filtered. The filtrate was evaporated and the product was isolated by silica gel column chromatography. Yield : 9.0g

b) 3,3-Bis (N-CBZ-L-valyloxymethyl)-propionic acid.

To a cooled solution of 4,4-bis (N-CBZ-L-valyloxymethyl)-but-1-ene (14.6g, 25 mmole) and tetrabutylammonium bromide (1.3g, 4 mmole) in 120ml benzene was added 100ml water. Under strong stirring potassium permanganate (15.8g, 100 mmole) was addded in portions and the mixture was stirred for 2 hours between 15°C and 20°C . A sodium bisulfite aqueous solution was added to the slurry until the mixture was discolored. The mixture was acidified with 2N hydrochloric acid and extracted four times with ethyl acetate. The organic phase was washed two times with water, dried with sodium sulfate and evaporated under reduced pressure . The product was isolated by silica gel column chromatography. Yield: 7.5g

^{1}H-NMR ($CDCl_3$) 0.89 (m, 12H) 2.05 (m, 2H) 2.46 (m, 2H) 2.62 (m, 1H) 4.20 (m, 6H) 5.11 (s, 4H) 5.30 (m, 2H) 7.35 (m, 10H)

Example AA-I-4

<u>2-(N-CBZ-L-valyloxy)-propionic acid</u>

a) 4-methoxybenzyl 2-hydroxypropionate.

To a stirred solution of DL -2 hydroxypropionic acid (9.0g , 100 mmole) in 100 ml dry DMF was added potassium tert-butoxide (12.34g, 110 mmole) and the mixture was stirred for one hour at 60°C. 4-methoxybenzyl chloride (18.8g 120 mmole) was added and the mixture was stirred for eight hours at 60°C. The mixture was

evaporated under reduced pressure and 250 ml ethyl acatate was added .The organic phase was washed four times with water. The organic phase was dried with sodium sulfate and concentrated in vacuo. Yield: 16.8g

b) 4-methoxybenzyl 2-(N-CBZ-L-valyloxy)propionate.

To a solution of 4-methoxybenzyl 2-hydroxypropionate (4.2g, 20 mmole), N-CBZ-L-valine (5.02g, 20 mmole) and DMAP (0.24g, 2 mmole) in 100 ml dichloromethane was added a solution of DCC (4.54g, 22 mmole) and the mixture was stirred overnight at room temperature. The mixture was cooled to 5°C and the urethane was filtered. The filtrate was evoporated and the product was isolated by silica gel column chromatography. Yield: 7.9g

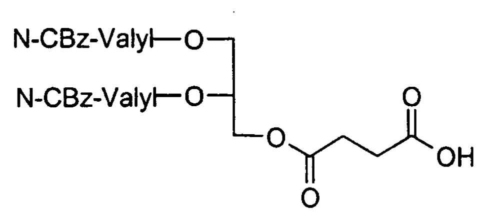
c) 2-(N-CBZ-L-valyloxy)-propionic acid.

To a solution of 4-methoxybenzyl 2-(N-CBZ-L-valyloxy)-propionate (7.8g, 17.5 mmole) in dichloromethane (100 ml) was added trifluoroacetic acid (10 ml) and the solution was stirred for one hour at room temperature. The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography.Yield: 5.0g

^{1}H-NMR ($CDCl_3$) 0.94 (m, 6H) 1.56 (d, 3H) 2.30 (m, 1H) 4.42 (m, 1H) 5.12-5.30 (m, 4H) 7.28 (m, 5H)

Example AA-I-5

Succinic acid 2,3-*bis*-(N-CBZ-L-valyloxy)propyl ester



a) 4-Methoxybenzyl succinate monoester.

To a mixture of succinic anhyride (75g, 750 mmole) and 4-methoxybenzyl alcohol (69.1g, 500 mmole) in 1,4-dioxane (300ml) was added pyridine (79.1g, 1000 mmole) and the mixture was stirred for five hours at 80°C . The mixture was evaporated

under reduced pressure and 600 ml of ethyl acetate and 60 ml of acetic acid were added. The organic phase was washed three times with water, dried with sodium sulfate and evaporated under reduced pressure. The product was recrystallized from toluene.Yield: 104 g.

b) Succinic acid 2,3-dihydroxy-propyl ester, 4-methoxybenzyl ester.

To a solution of glycerol (23.0g, 250 mmole), 4-methoxybenzyl succinate monoester (5.96 g, 25 mmole) and DMAP (0.36g, 3 mmole) in DMF (200ml) was added DCC (6.2g 30 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and 150ml dichloromethane was added. The mixture was filtered and the solution washed twice with water. The water phase was extracted two times with dichloromethane and the combined organic phases were dried with sodium sulfate. The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography.
Yield: 3.0g

c) Succinic acid 2,3-*bis*-(N-CBZ-L-valyloxy)-propyl ester, 4-methoxybenzyl ester.

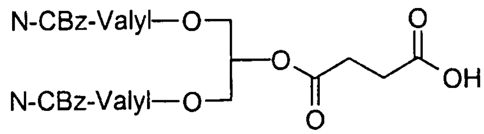
To a stirred solution of succinic acid 2,3-dihydroxy-propyl ester, 4-methoxybenzyl ester (2.9g, 9.28 mmole), N-CBZ-L-valine (5.03g, 20 mmole) and DMAP (0.244g, 2 mmole) in dichloromethane (60ml) was added DCC (4.5g, 22 mmole) and the mixture was stirred overnight at room temperature. The mixture was filtered and the solution was evaporated under reduced pressure. The product was isolated by silica gel column chromatography.Yield: 2.5g

d) Succinic acid 2,3-*bis*-(N-CBZ-L-valyloxy)propyl ester.

To a solution of the above intermediate (2.3g, 2.95 mmole) in dichloromethane (25ml) was added trifluoroacetic acid (2.5ml) and the solution was stirred for two hours at roomtemperature. The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography. Yield: 1,8g
^{1}H-NMR ($CDCl_3$) 0.92 (m, 12H) 2.12 (m, 2H) 2.64 (m, 4H) 4.32 (m, 4H) 5.10 (s, 4H) 5.22-5.50 (m, 3H) 7.34 (m, 10H)

Example AA-I-6

Succinic acid 1,3-*bis*-(N-CBZ-L-valyloxy)-2-propyl ester



a) Succinic acid 1,3-dibromo-2-propyl ester, 4-methoxybenzyl ester.

To a solution of 1,3-dibromopropan-2-ol (21.8g, 100 mmole), succinic acid 4-methoxybenzyl ester (28.6g,120 mmole) and DMAP (1.22g, 10 mmole) in dichloromethane (400ml) was added DCC (24.8g, 120 mmole) in portions at about 10°C. The mixture was stirred overnight at room temperature and cooled to about 5°C. The mixture was filtered and the solution was evaporated under reduced pressure. 600ml of ethyl acetate was added and the organic phase was washed twice with 5% acetic acid, 5% sodium hydrogen carbonate and water. The solution was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography.Yield: 34.8g.

b) Succinic acid 1,3-*bis*-(N-CBZ-L-valyloxy)-2-propyl ester, 4-methoxybenzyl ester.

To a solution of N-CBZ-L-valine (58.5 g, 232.8 mmole) in dried DMF (300ml) was added potassium-tert.-butoxide (24,68 g, 220 mmole) and the mixture was stirred for one hour at room temperature. A solution of succinic acid 1,3-dibromo-2-propyl ester, 4-methoxybenzyl ester (34 g, 77.6 mmole) in dried DMF (50ml) was added and the mixture was stirred for eighteen hours at 60°C. The potassium bromide was filtered and the solution was evaporated under reduced pressure. 600ml of ethyl acetate was added and the organic phase washed twice with 5% sodium hydrogen carbonate and with water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography.Yield: 45g

c) Succinic acid 1,3-*bis*-(N-CBZ-L-valyloxy)-2-propyl ester.

To a cooled solution of the intermediate immediately above (44.5 g, 57.1 mmole) in dichloromethane (500ml) was added trifluoroacetic acid (50ml) between 5°C and 10°C and the solution was stirred for two hours at 10°C. The solution was evaporated under reduced pressure and two times coevaporated with toluene. 400ml of ethanol was added and the mixture was stirred for 30 minutes at 40°C. The mixture was cooled and the biproduct filtered. The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography.

Yield: 33g

^{1}H-NMR (DMSO-d6) 0.88 (m, 12H) 2.04 (m, 2H) 2.46 (m, 4H) 3.94-4.40 (m, 6H) 5.02 (s, 4H) 5.18 (m, 1H) 7.32 (m, 10H) 7,74 (d , 2H)

Example AA-I-7

<u>Alternative route to succinic acid 1,3-*bis*-(N-CBZ-L-valyloxy)-2-propyl ester</u>

a) Succinic acid 1,3-dibromo-2-propyl ester, 1,1-dimethylethyl ester.

To a solution of 1,3-dibromopropan-2-ol (10.9 g 50 mmole), succinic acid 1,1-dimethylethyl ester (J. Org.Chem 59 (1994) 4864) (10.45g, 60 mmole) and DMAP (0.61 g, 5 mmole) in dichloromethane (180ml) was added DCC (12.4 g, 60 mmole) in portions at about 10°C. The mixture was stirred overnight at room temperature and cooled to about 5°C. The mixture was filtered and the solution was evaporated under reduced pressure. 250ml ethyl acetate was added and the organic phase was washed twice with 5% citric acid, 5% sodium hydrogen carbonate and water. The solution was dried with sodium sulfate and evaporated under reduced pressure. The product was distilled in vacuo. (bp 0,5 135-140°C) Yield: 16.8 g

b) Succinic acid 1,3-*bis*-(N-CBZ-L-valyloxy)-2-propyl ester, 1,1-dimethylethyl ester.

To a solution of N-CBZ-L-valine (18.85 g, 75 mmole) in dried DMF (100ml) was added potassium tert.-butoxide (7.85 g, 70 mmole) and the mixture was stirred for one hour at room temperature. A solution of succinic acid 1,3-dibromo-2-propyl ester, 1,1-dimethylethyl ester (9.35g, 25 mmole) in dried DMF (20ml) was added and the mixture was stirred for eighteen hours at 60°C. The potassium bromide was filtered and the solution evaporated under reduced pressure. 300ml of ethyl acetate

were added and the organic phase washed twice with 5% sodium hydrogen carbonate and with water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 14g

c) 1,3-*bis*-(N-CBZ-L-valyloxy)-2-propyl succinate monoester.
To a cooled solution of succinic acid 1,3-bis-(N-CBZ-L-valyloxy)-2-propyl ester, 1,1-dimethylethyl ester (13 g, 18.18 mmole) in dichloromethane (100ml) was added trifluoroacetic acid (20ml) and the solution was stirred for six hours at room temperature. The solution was evaporated under reduced pressure. 200ml ethyl acetate was added and the organic phase was washed with 5% sodium hydrogen carbonate and water. The solution was evaporated under reduced pressure.
Yield: 11.7g

Example AA-1-8
<u>3-benzyloxycarbonylpropionic acid chloromethyl ester</u>

a) Succinic acid monobenzyl ester
Succinic anhydride (30 g, 300 mmole) was dissolved in methylene chloride (300 ml). To the solution were added benzyl alcohol (10.2 ml, 100 mmole), 4-dimethylaminopyridine (1.22 g, 10 mmole) and pyridine (48 ml). After 3 hours the reaction mixture was poured in to citric acid aqueous solution. The organic phase was concentrated to small volume and sodium hydrogen carbonate and water were added. Then mixture was stirred for 30 min. The aqueous phase was collected, and to it was added citric acid aqueous solution. The product precipitated out, was collected and dried. 15.3 g.

b) 3-benzyloxycarbonylpropionic acid chloromethyl ester
Succinic acid monobenzyl ester (4.16 g, 20 mmole) was dissolved in dioxane (20 ml). To the solution was added tetrabutylammonium hydroxide aqueous solution (40 %, 11.6 ml, 18 mmole). The solution was dried in vacuo and coevaporated with toluene several times. The residue was dissolved in methylene chloride (60 ml) and then chloroiodomethane (14.5 ml, 200 mmole) was added to the solution. The

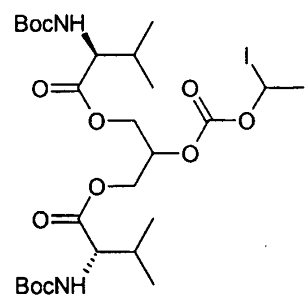
reaction solution was stirred for 18 hr and then evaporated and the product was isolated with silica gel column chromatography. 3.64 g

c) 3-Benzyloxycarbonylpropionic acid iodomethyl ester.

3-Benzyloxycarbonylpropionic acid chloromethyl ester (2 g, 1.38 mmole) was dissolved in acetonitrile (30 ml). Sodium iodide (1.6 g, 10.9 mmole) was added to the solution. After reaction at 70° C for 3 hr, the reaction mixture was filtered and the residue was dissolved in methylene chloride (20 ml) and refiltered. The solution was dried and gave intermediate 3-benzyloxycarbonylpropionic acid iodomethyl ester in quantitative yield. This intermediate is bonded to an accessible function of a drug, such as a ring hydroxy or carboxy function using conventional alkylation/acylation conditions as described generally herein. Following deprotection of the terminal carboxy, a di/trifunctional linker bearing R_2, such as 1,3-bis- O-(L-valyl)glycerol or iodomethyloxy-L-valyl is acylated/alkylated thereon or R_2 amide bonded thereon by conventional techniques as described herein, such as with DCC coupling agent.

Example AA-I-9

<u>1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl 1-iodoethyl carbonate</u>



(a) 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl 1-chloroethyl carbonate.

To a solution of 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propanol (0.545 g, 1.11 mmol) in 5 mL dry CH_2Cl_2 were added pyridine (540 μL, 6.68 mmol), with cooling and stirring in an ice bath, followed by 1-chloroethyl chloroformate (242 μL, 2.22 mmol). After 1 h, the reaction mixture was diluted with 5 mL CH_2Cl_2 and washed with water (5 mL) and brine (5 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated on a rotavapor, coevapoating several times with

toluene. Column chromatogaphy (silica, 4/1 petroleum ether - ethyl acetate) gave the chloride (596 mg, 90%) as a white solid.

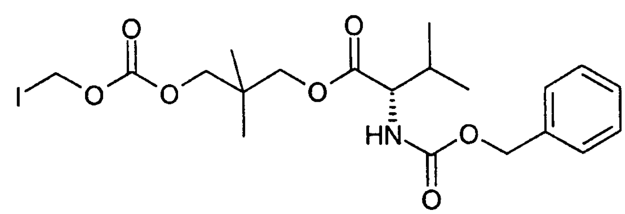
(b) 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl 1-iodoethyl carbonate.

A mixture of the chloride (596 mg, 1.0 mmol) from step (a) and NaI (684 mg, 4.57 mmol) in 10 ml dry MeCN was refluxed at 80 °C for 4 h. The reaction mixture was concentrated under vacuum and then partitioned between 30 mL diethyl ether and 10 mL water. The organic phase was washed with 5% aqueous sodium thiosulfate (2 x 5 mL), and the last aqueous layer was reextracted with ether (5 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (silica, 4/1 petroleum ether – ethyl acetate) gave a fraction (275 mg) containing 80% iodide, as determined from ^{1}H NMR, and small amounts of the starting chloride and alkene from the elimination side reaction.

^{1}H NMR (250 MHz, $CDCl_3$) δ 0.81-0.85 (m, 6H), 0.88-0.92 (m, 6H), 1.37 (s, 18H), 2.05 (m, 2H), 2.17 (d, 3H, J = 6.1 Hz), 4.12-4.46 (m, 6H), 5.00 (d, 2H, J = 8.8 Hz), 5.11 (m, 1H), 6.68 and 6.69 (2 sets of q, 1H, J = 6.1 Hz).

Example A-I-10

3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethylpropyl iodomethyl carbonate



(a) 3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethyl-1-propanol.

A mixture of *N*-benzyloxycarbonyl-L-valine (2.50 g, 10.0 mmol), 2,2-dimethyl-1,3-propanediol (5.30 g, 50.9 mmol), dicyclohexylcarbodiimide (2.60 g, 12.6 mmol), and 4-dimethylaminopyridine (125 mg, 1.0 mmol) in 100 mL dry CH_2Cl_2 was stirred for 23 h. The reaction mixture was filtered and washed successively with 50 mL each of water, saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The title compound (2.99

g, 87%) was isolated by flash column chromatography (silica, 2/1 petroleum ether – ethyl acetate) as a white waxy solid.

(b) 3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethylpropyl chloromethyl carbonate

Chloromethyl chloroformate (1.50 mL, 16.6 mmol) was added to a solution of the alcohol (2.74 g, 8.12 mmol) from step (a) and pyridine (4.9 mL, 61 mmol) in 40 mL dry CH_2Cl_2, in an ice bath. After stirring for 1 h, the mixture was diluted with CH_2Cl_2 and washed successively with water, saturated $NaHCO_3$, and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated, coevaporating several times with toluene on a rotavapor. Flash column chromatography (silica, 2/1 petroleum ether – ethyl acetate) gave 3.31 g (95%) of the title compound.

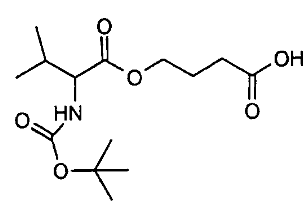
(c) 3-(*N*-benzyloxycarbonyl-L-valyloxy)-2,2-dimethylpropyl iodomethyl carbonate

A mixture of the chloride (3.14 g, 7.30 mmol) from step (b) and NaI (4.37 g, 29.2 mmol) in 73 mL dry MeCN was refluxed at 80 °C for 3 h. After removal of solvent under vacuum, the mixture was partitioned between 80 mL ethyl acetate and 40 mL water. The organic phase was washed with 5% $Na_2S_2O_3$, and then brine, dried over anhydrous Na_2SO_4, and concentrated. Flash column chromatography (silica, petroleum ether – ethyl acetate) gave 3.68 g (97%) of the title compound.

^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 and 0.96 (2d, 3H each), 0.98 (s, 6H), 2.18 (m, 1H), 3.94 and 4.02 (2s, 2H each), 4.32 (dd, 1H, J = 9.0, 4.7 Hz), 5.11 (s, 2H), 5.26 (d, 1H), 5.92 and 5.93 (ABq, 2H, J_{AB} = 5.1Hz), 7.35 (s, 5H).

Example AA-I-11

4-(N-Boc-L-valyloxy)butyric acid



a) Preparation of 4-bromobutyric acid benzyl ester

4-bromobutyric acid (10.6g, 60 mmole) was dissolved in thionyl chloride (20 mml), and the reaction was kept for 4 hr. The solution was evaporated and coevaporated with toluene several times. The residue was redissolved in dichloromethane (120 ml), and then benzyl alcohol (4.14 ml, 40 mmole) was added. The solution was cooled down to -50° C and triethylamine (10 ml, 72 mmole) was added. The reaction mixture was slowly warmed to room temperature. After 3 hr, the reaction mixture was poured into sodium bicarbonate aqueous solution and the organic phase was washed with water and dried, giving the titled product, 6.8 g.

b) Preparation of 4-(N-Boc-L-valyloxy)butyric acid benzyl ester

N-Boc-L-valine (1.3 g, 6 mmole) was dissolved in dioxane (5 ml). To the solution was added tetrabutylammonium hydroxide aqueous solution (40 %, 3.8 ml, 6 mmole), and the solution was evaporated and coevaporated with toluene several times. The residue was dissolved in DMF (15 ml) and 4-bromobutyric acid benzyl ester (1.28g, 5mmole) was added to it. The reaction was kept for 18 hr, and then poured into sodium bicarbonate aqueous solution and extracted with dichloromethane. The organic phase was dried and the product was isolated with silica gel column chromatography, 1.2 g.

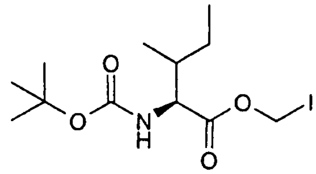
c) 4-(N-Boc-L-valyloxy)butyric acid.

To a solution of 4-(N-Boc-L-valyloxy)butyric acid benzyl ester (1.2 g , 3 mmole) in ethyl acetate/methanol (5ml/5ml) was added palladium black (20 mg). The reaction mixture was kept under hydrogen at atmospheric pressure for 2 hr. The suspension was filtered through Celite and dried, giving the title product, 840 mg.

^{1}H-NMR ($CDCl_3$): 5.05 (d, 1H) 4.20 (m, 3H) 2.48 (t, 2H) 2.00 (m, 2H) 1.46 (s, 9H) 0.96 (m, 6H).

Example AA-I-12

<u>N-BOC-L-isoleucine iodomethyl ester</u>



a) N-BOC-L-isoleucine chloromethyl ester.

To a solution of N-BOC-L-isoleucine (23.1 g, 0.1 mol) in dioxane (500 mL), was added dropwise a 40% aqueous solution of tetrabutylammonium hydroxide (65.6 mL, 0.1 mol). After stirring for 15 min, the solution was evaporated to dryness through co-evaporation with dioxane and toluene. The residue was dissolved in dichloromethane (500 mL) and then chloroiodomethane (72.8 mL, 1 mol) was added and the solution was stirred for 6h at room temperature. The solution was concentrated under reduced pressure and the residue was shaken with hexane / ethyl acetate (1:1 v/v, 400 mL). The yellow crystalline solid was filtered off and the filtrate was washed with aqueous solution of sodium thiosulfate (0.1 M) and then filtered through anhydrous sodium sulfate and evaporated to dryness. The residue was column chromatographed (silica gel, 1-2% MeOH in CH_2Cl_2), to give 20.8 g of N-BOC-L-isoleucine chloromethyl ester.

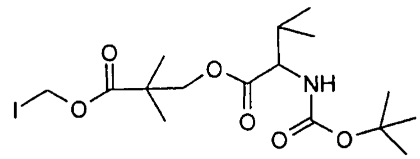
b) N-BOC-L-isoleucine iodomethyl ester.

To a solution of N-BOC-L-isoleucine chloromethyl ester (19.6 g, 70 mmol) in acetonitrile (300 mL), was added sodium iodide (31.5 g, 210 mmol). The solution was stirred for 4 h at 60 °C. The resulting suspension was filtered and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and washed with aqueous sodium thiosulfate (0.1 M). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 2% MeOH in CH_2Cl_2), to give 22.6 g of N-BOC-L-isoleucine iodomethyl ester.

^{1}H-NMR ($CDCl_3$): 6.04 (d, 1H), 5.82 (d, 1H), 4.97 (d, 1H), 4.25 (dd, 1H), 1.98-1.80 (m, 1H), 1.43 (s, 9H), 1.50-1.05 (m, 2H), 0.97-0.88 (m, 6H).

Example AA-I-13

2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid iodomethyl ester



a) 2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid:

N-Boc-L-valine (10.8g, 50 mmole), 4-dimethylaminopyridine (610 mg, 5 mmole) and DCC (6.18 g, 30 mmole) were dissolved in methylene chloride (100 ml). After stirring for 2 hour the mixture was filtered. To the filtrate were added 2,2-dimethyl-3-hydroxy-propionic acid (3.54g, 30 mmole) and pyridine (10 ml). After 18 hr, the reaction mixture was filtered, and the filtrate was poured into sodium hydrogen carbonate aqueous solution, the organic phase was then washed with citric acid aqueous solution and water succesively. After evaporation the product was isolated with silica gel column chromatography to yield 4.4g. This compound can be activated and esterified directly to a drug or further modified as described below.

b) 2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid chloromethyl ester .

2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid (3.9 g, 12.3 mmole) was dissolved in dioxane (60 ml). To the solution was added tetrabutylammonium hydroxide aqueous solution (40 %, 7.78 ml, 12 mmole). The solution was dried in vacuo, and it was coevaporated with toluene for several times. The residue was dissolved in methylene chloride and then chloroiodomethane (18.9 ml, 260 mmole) was added to the solution. After 18 hr, the reaction solution was evaporated and the product was isolated with silica gel column chromatography to yield 3.7 g.

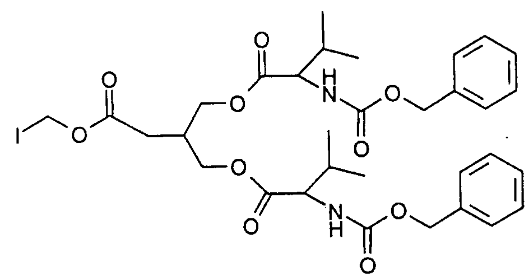
c) 2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid iodomethyl ester .

2,2-Dimethyl-3-(N-Boc-L-valyloxy)propionic acid chloromethyl ester (3.6 g, 10 mmole) was dissolved in acetonitrile (50 ml). Sodium iodide (2.1 g, 14 mmole) was added to the solution. After reaction at 70° C for 2 hr, the reaction mixture was filtered and the residue was dissolved in methylene chloride (20 ml) and refiltered. The solution was dried and gave 4.34g of the titled product..

^{1}H-NMR ($CDCl_3$): 5.92 (dd, 2H) 5.10 (d, 1H) 4.24 (m, 1H) 4.15 (dd, 2H) 2.01 (m, 1H) 1.44 (s, 9H) 1.25 (d, 6H) 0.91 (m, 6H)

Example AA-I-14

3,3- bis (N-CBz-L-valyloxymethyl)-propionic acid iodomethyl ester



a) Preparation of 3,3-bis (N-CBz-L-valyloxymethyl)-propionic acid chloromethyl ester.

3,3- bis (N-CBz-L-valyloxymethyl)-propionic acid (3 g, 5 mmole) was dissolved in dioxane (20 ml). To the solution was added tetrabutylammonium hydroxide aqueous solution (40 %, 3.11 ml, 4.8 mmole). The solution was dried in vacuo, and it was coevaporated with toluene several times. The residue was dissolved in methylene chloride (15 ml) and then chloroiodomethane (7.3 ml, 100 mmole) was added to the solution. The reaction solution was refluxed for 18 hr and then evaporated and the product was isolated with silica gel column chromatography. 900 mg.

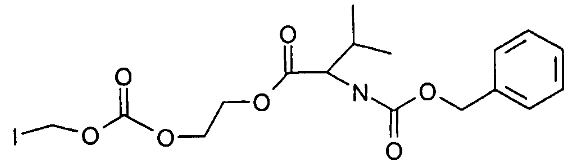
b) 3,3-bis-(N-CBz-L-valyloxymethyl)propionic acid iodomethyl ester.

3,3-bis (N-CBz-L-valyloxymethyl)-propionic acid chloromethyl ester (900 mg, 1.38 mmole) was dissolved in acetonitrile (5 ml). Sodium iodide (289 mg, 1.93 mmole) was added to the solution. After reaction at 70° C for 3 hr, the reaction mixture was filtered and the residue was dissolved in methylene chloride (5 ml) and refiltered. The solution was dried and gave the titled product. 800 mg.

^{1}H-NMR ($CDCl_3$): 7.35 (m, 10 H) 5.88 (dd, 2H) 5.25 (d, 2H) 4.29 (m, 2H) 4.18 (m, 4H) 2.56 (m, 1H) 2.42 (d, 2H) 2.16 (m, 2H) 0.93 (m 12 H)

Example AA-I-15

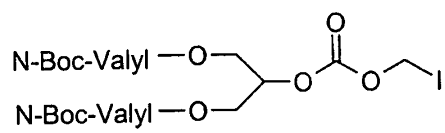
2-(N-CBz-L-valyloxy)ethoxycarbonyloxymethyl iodide



2-(N-CBz-L-valyloxy)ethoxycarbonyloxymethyl chloride (1.16 g, 3 mmole) was dissolved in acetonitrile (10 ml). Sodium iodide (630 g, 4.2 mmole) was added to the solution. After reaction at 65° C for 2.5 hr, the reaction mixture was cooled down to room temperature and filtered and the residue was dissolved in methylene chloride (5 ml) and refiltered. The solution was dried and gave the titled product. 1.2 g. ^{1}H-NMR ($CDCl_3$): 7.35 (m, 5H) 5.93 (dd, 2H) 5.26 (d, 1H) 5.11 (s, 2H) 4.39 (m, 5H) 2.18 (m, 1H) 0.94 (m, 6 H).

Example AA-I-16

1,3-bis(N-tert-butoxycarbonyl-L-valyloxy)-2-propyl iodomethyl carbonate)



a) 1-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol

N-tert-Butoxycarbonyl-L-valine (32.53 g, 0.150 mol), *N,N'*-dicyclohexyl-carbodiimide (37.85 g, 0.183 mol, and 4-dimethylaminopyridine (1.83 g, 0.015 mol) were added to glycerol (138.12 g., 1.5 mol) in 500 mL dry DMF and the mixture was stirred at rt under N_2 for 3 days. The reaction mixture was filtered, concentrated under vacuum, and then partitioned between 300 mL EtOAc and 150 mL H_2O. The aqueous phase was reextracted with 150 mL EtOAc. The organic phases were combined and washed successively with 100 mL each of saturated aqueous $NaHCO_3$, saturated NH_4Cl, and brine. Drying over anhydrous Na_2SO4, and concentration under vacuum gave a viscous light yellow oil as crude product. Flash column chromatography on silica gel with 4/1 EtOAc - petroleum ether (BP 40-60 °C) gave 18.27 g (42%) of product (alternative nomenclature: 3-(N-tert-butoxycarbonyl-L-valyloxy)-1,2-propanediol). Reactions done overnight gave similar yields.

b) 1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol

1-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol (17.95 g. 61.6 mmol), Boc-L-valine (6.69 g, 30.8 mmol), DMAP (0.38 g, 3.1 mmol), and DCC (7.10 g, 34.4 mmol) in 240 mL CH_2Cl_2 and 60 mL DMF were stirred at rt under N_2 for 18 h. The reaction mixture was filtered, concentrated under vacuum, and redissolved in 200 mL EtOAc. The organic solution was washed with 50 mL saturated NH_4Cl. The aqueous phase was reextracted with 50 mL EtOAc. The organic phases were combined, washed successively with 50 mL saturated $NaHCO_3$ and 50 mL brine, dried over Na_2SO_4, and concentrated under vacuum. Flash column chromatography of the crude material on silica gel (eluent 2/1 petroleum ether – EtOAc, and then EtOAc) gave 7.41 g (49%) of the title compound (alternative nomenclature: 1,3-bis(N-tert-butoxycarbonyl-L-valyloxy)-2-propanol).

c) 2-*O*-chloromethoxycarbonyl-1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol. Chloromethyl chloroformate (2.70 mL, 30 mmol) was added to a solution of 1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol (7.27 g, 14.8 mmol) and pyridine (7.2 mL, 89 mmol) in 60 mL dry CH_2Cl_2, in an ice bath, under N_2. After stirring for 1 h 45 min, the reaction mixture was diluted with 100 mL CH_2Cl_2 and washed with 40 mL water. The aqueous phase was reextracted with 20 mL H_2O. The organic phases were combined, washed with 40 mL saturated $NaHCO_3$, followed by 2 x 50 mL brine, dried over Na_2SO_4, and concentrated under vacuum. Flash column chromatography on silica gel with 2/1 hexane- EtOAc gave 8.03 g (93%) of the title compound (alternative nomenclature: 1,3-bis(N-tert-butoxycarbonyl-L-valyloxy)-2-propyl chloromethyl carbonate).

d) 2-*O*-iodomethoxycarbonyl-1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol.

A solution of 2-*O*-chloromethoxycarbonyl-1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)propane-1,2,3-triol (7.86 g, 13.5 mmol) and NaI (8.09 g, 54.0 mmol) in 135 mL dry acetonitirile was refluxed at 80 °C for 4 h under N_2. The reaction mixture was concentrated under vacuum, and then partitioned between 150 mL diethyl ether and 50 mL H_2O. The aqueous layer was reextracted with 2 x 25 mL ether. The combined organic phases were washed successively with 25 mL aqueous $Na_2S_2O_3$ and 50 mL

brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (silica gel, 2/1 hexane-ethyl acetate gave 8.38 g (92%) title product (alternative name: 2-iodomethoxycarbonyloxy-1,3-bis-(*N*-tert-butoxycarbonyl-L-valyloxy)propane or 1,3-bis(N-tert-butoxycarbonyl-L-valyloxy)-2-propyl iodomethyl carbonate) as a white solid.^{1}H NMR (250 MHz, $CDCl_3$) δ 0.81 (d, 6H), 0.88 (m, 6H), 1.36 (s, 18H), 2.06 (m, 2H), 4.11-4.46 (m, 6H), 5.0 (br d, 2H), 5.12 (m, 1H), 5.88 (s, 2H).

Example A-I-1

Iodomethyl 2-methyl-2-(N-benzyloxycarbonyl-L-valyloxymethyl) propionate

a) 4-Methoxybenzyl 2-(hydroxymethyl)-2-methyl propionate.

2-(Hydroxymethyl)-2-methyl propionic acid was esterified by alkylation with 4-methoxybenzyl chloride by conventional means, namely treatment with aqueous NaOH, followed by evaporation and dissolution in an organic solvent such as DMF to which the 4-methoxybenzyl chloride is added and the reaction warmed and agitated, such as stirring at 60 C for one hour. The reaction mixture is cooled, concentrated by rotavapor and the resulting concentrated suspension partitioned between water and dichloromethane. The organic phase is evaporated and the reside subjected to silica gel column chromatography, for example with 0, 2, 4% EtOH in dichloromethane to yield the title compound (7.10 g). R_f (2%MeOH/$CHCl_3$) 0.40.

b) 4-Methoxybenzyl 2-(N- benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate.

4-Methoxybenzyl 2-(hydroxymethyl)-2-methyl propionate (2.50 g, 10.5 mmol), N-benzyloxy carbonyl-L-valine (2.51 g, 10 mmole), 4-dimethylaminopyridine (183 mg) and 1-hydroxybenzotriazole (1.35g, 10 mmole) were mixed and dissolved in N,N-dimethylformamide (90 ml). Then dicyclohexyl-carbodiimide (2.47 g 12 mmol) was added. After stirring for 3 days at room temperature the suspension was filtered and the filtrate evaporated in vacuo. The residue was partitioned between 0.1M citric acid and dichloromethane. The organic phase was then extracted with aqueous saturated $NaHCO_3$ and evaporated in vacuo. The residue was silica gel column chromatographed (0, 1, 2, 3% ethanol in dichloromethane). The appropriate fractions were pooled and evaporated in vacuo to give the title compound (2.72 g).

d) 2-(N- benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionic acid.

To a solution of 4-methoxybenzyl 2-(N- benzyloxycarbonyl -L-valyloxymethyl)-2-methyl propionate (2.72 g, 5.76 mmole), was added trifluoroacetic acid (11.5 ml) and the emerging dark red solution was stirred for 30 min at room temperature. The solution was evaporated to dryness with dioxane and toluene. The residue was silica gel column chromatographed (2, 3, 4% ethanol in dichloromethane). The appropriate fractions were pooled and evaporated in vacuo to give the title compound (1.86 g). The compound can be activated and esterified direct to a drug or further modified as described below. R_f (2%MeOH/$CHCl_3$) 0.30.

^{1}H-NMR ($CDCl_3$): 7.32 (s, 5H), 5.32 (d, 1H), 5.10 (s, 2H), 4.32 (d,d, 1H), 4.21 (d,d, 2H), 2.13 (m, 1H), 1.26 (s, 3H), 1.25 (s, 3H), 0.95 (d, 3H), 0.86 (d, 3H).

c) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate.

2-(N- benzyloxycarbonyl -L-valyloxymethyl)-2-methyl propionic acid was esterified by conventional techniques, namely dissolution in an organic solvent such as dioxane and dropwise addition of aqueous tetrabutylammonium hydroxide, followed by evaporation. The residue is dissolved in dichloromethane and then chloroiodomethane and the mixture stirred for 6 hours at room temperature, followed by partition, shaking the filtrate with aqueous sodium thiosulphate. 0.1M, filtration and evaporation. The title compound (1.40 g) was obtained after silica gel column chromatography (0, 1, 2, 3% ethanol in dichloromethane).

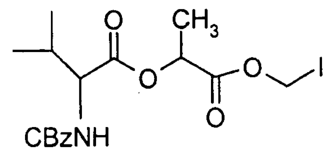
c) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate.

Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate was converted to iodide by conventional techniques, namely addition to NaI in acetonitrile, stirring and heating, for instance to 75 C for four hours. The resulting suspension is filtered and the filtrate evaporated, dissolved in organic solvent such as toluene and shaken with aqueous sodium thiosulphate (0.1M) and evaporation to give the title compound (1.25 g) practically pure. R_f (2%MeOH/$CHCl_3$) 0.80.

^{1}H-NMR ($CDCl_3$): 7.35 (s, 5H), 5.90 (d,d, 2H), 5.24 (d, 1H), 5.10 (s, 2H), 4.31 (d,d, 1H), 4.14 (d,d, 2H), 2.16 (m, 1H), 1.22 (s, 6H), 0.96 (d, 3H), 0.87 (d, 3H).

Example A-I-2

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-DL-propionate.

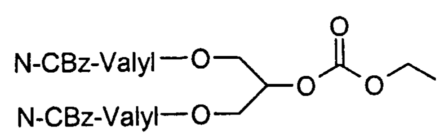


a) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-DL-propionate.
2-(N-benzyloxycarbonyl-L-valyloxy) propionic acid (1 g) was esterified by the method described in Example A-I-I, step d. The title compound (0.76 g) was obtained after silica gel column chromatography (0, 1% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.75.

b) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-DL-propionate
Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-methyl propionate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (0.95 g) practically pure. R_f (2%MeOH/$CHCl_3$) 0.75.
^{1}H-NMR ($CDCl_3$): 7.33 (s, 5H), 5.98 (d, 1H), 5.86 (d, 1H), 5.26 (d, 1H), 5.10 (s, 2H), 5.07 (q, 1H), 4.38 (d,d, 1H), 2.30 (m, 1H), 1.49 (d, 3H), 1.03 (d, 3H), 0.95 (d, 3H).

Example A-I-3

Iodomethyl (1,3-di-(N-benzyloxycarbonyl)-L-valyloxy)-2-propyl carbonate.



a) Chloromethyl (1,3-di-(N-benzyloxycarbonyl)-L-valyloxy)-2-propyl carbonate.
To a solution of 1,3-di-((N-benzyloxycarbonyl)-L-valyloxy)propan-2-ol (1.34 g, 2.4 mmole) in dichloromethane (10 ml) was added dry pyridine (1.15 ml, 14.4 mmol)

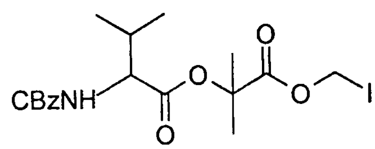
and chloromethyl chloroformate (0.43 ml, 4.8 mmole) at 0°C. The reaction was then stirred for 30 min and then poured into aqueous 50% saturated sodium chloride / 0.1M citric acid solution and extracted with dichloromethane. The organic phase was evaporated and the residue silica gel column chromatographed (0, 1, 1.5% ethanol in dichloromethane). The appropriate fractions were pooled and evaporated in vacuo to give the title compound (1.26g). R_f (2%MeOH/ $CHCl_3$) 0.85.

b) Preparation of iodomethyl (1,3-di-(N-benzyloxycarbonyl)-L-valyloxy)-2-propyl carbonate.

Chloromethyl (1,3-di-(N-benzyloxycarbonyl)valyloxy)-2-propyl carbonate was converted to iodide by the method described in Example A-I-1, step e) to give the title compound (1.37 g) practically pure. R_f (2%MeOH/$CHCl_3$) 0.85.
^{1}H-NMR ($CDCl_3$): 7.34 (s, 10H), 5.93 (d, 1H), 5.89 (d, 1H), 5.21 (m, 3H), 5.11 (s, 4H), 4.50-4.17 (m, 6H), 2.12 (m, 2H), 0.97 (d, 6H), 0.88 (d, 6H).

Example A-I-4

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)isobutyrate.



a) 4-Methoxybenzyl 2-hydroxyisobutyrate.

2-hydroxy isobutyric acid (1.56 g) was esterified by alkylation with 4-methoxybenzyl chloride by the method described in Example A-I-1, step a). The title compound (2.65 g) was obtained after silica gel column chromatography (0, 1, 2% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.45.

b) 4-Methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate.

4-methoxybenzyl 2-hydroxyisobutyrate was acylated with N-benzyloxycarbonyl-L-valine by the method described in Example A-I-1, step b). The title compound (3.21 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.70.

c) 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyric acid.

4-methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate was de-esterified by the method described in Example A-I-1 step c. The title compound (2.01 g) was obtained after silica gel column chromatography (2, 10, 20% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.30. This compound may be activated and esterified directly to a drug, or further modified as described below.

^{1}H-NMR ($CDCl_3$): 7.32 (s, 5H), 5.33 (d, 1H), 5.10 (s, 2H), 4.31 (d,d, 1H), 2.22 (m, 1H), 1.57 (s, 6H), 0.98 (d, 3H), 0.89 (d, 3H).

d) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate.

2-(N-benzyloxycarbonyl-L-valyloxy) isobutyric acid was esterified by the method described in Example A-I-1, step d. The title compound (1.90 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.80.

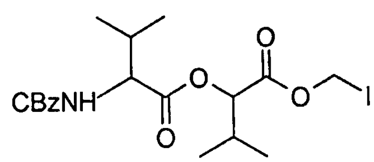
e) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate.

Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy) isobutyrate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (2.32 g) practically pure. R_f (2%MeOH/$CHCl_3$) 0.80.

^{1}H-NMR ($CDCl_3$): 7.33 (s, 5H), 5.89 (s, 2H), 5.22 (d, 1H), 5.11 (s, 2H), 4.29 (d,d, 1H), 2.21 (m, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.00 (d, 3H), 0.93 (d, 3H).

EXAMPLE A-I-5

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate.



a) 4-Methoxybenzyl 2-hydroxy-3-methyl-(S)-(+)-butyrate.

2-hydroxy-3-methyl-(S)-(+)-butyric acid (1.77 g) was esterified by alkylation with 4-methoxybenzyl chloride by the method described in Example A-I-1, step a. The title

compound (3.10 g) was obtained after silica gel column chromatography (0, 1, 2% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.50.

b) 4-Methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

4-Methoxybenzyl 2-hydroxy-3-methyl-(S)-(+)-butyrate was acylated with N-benzyloxycarbonyl-L-valine by the method described in Example A-I-1, step b. The title compound (5.74 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.70.

c) 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyric acid.

4-methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate was de-esterified by the method described in Example A-I-1, step c. The title compound (3.41 g) was obtained after silica gel column chromatography (2, 10, 20% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.45. The compound may be activated and esterified directly to a drug or further modified as described below:

^{1}H-NMR ($CDCl_3$): 7.36 (s, 5H), 5.38 (d, 1H), 5.11 (s, 4H), 4.90 (d, 1H), 4.41 (d,d, 1H), 2.28 (m, 2H), 1.04-0.89 (m, 12H).

d) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyric acid was esterified by the method described in Example A-I-1, step d. The title compound (2.96 g) was obtained after silica gel column chromatography (0, 1, 2% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.85.

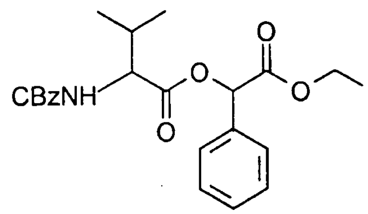
e) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-3-methyl-(S)-(+)-butyrate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (3.64 g) practically pure. R_f (2%MeOH/$CHCl_3$) 0.85.

^{1}H-NMR ($CDCl_3$): 7.36 (s, 5H), 6.00 (d, 1H), 5.83 (d, 1H), 5.28 (d, 1H), 5.11 (s, 4H), 4.83 (d, 1H), 4.41 (d,d, 1H), 2.29 (m, 2H), 1.05-0.90 (m, 12H).

EXAMPLE A-I-6

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate.



a) 4-Methoxybenzyl 2-hydroxy-2-phenyl-DL-acetate.

DL-mandelic acid (2.28 g) was esterified by alkylation with 4-methoxybenzyl chloride by the method described in Example A-I-1, step a. The title compound (3.69 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.55.

b) 4-Methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate.

4-Methoxybenzyl 2-hydroxy-2-phenyl-DL-acetate was acylated with N-benzyloxycarbonyl-L-valine by the method described in Example A-I-1, step b. The title compound (6.50 g) was obtained after silica gel column chromatography (0, 1, 1.5% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.75.

c) 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetic acid.

4-Methoxybenzyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate was de-esterified by the method described in Example A-I-1, step c. The title compound (4.75 g) was obtained after silica gel column chromatography (2, 10, 20% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.40. The compound may be activated and esterified directly to a drug or further modified as described below.

^{1}H-NMR ($CDCl_3$): 7.36 (m, 10H), 5.91 (d, 1H), 5.27 (m, 1H), 5.04 (s, 2H), 4.57-4.40 (2xd,d, 1H), 2.30 (m, 1H), 1.01-0.82 (m, 6H).

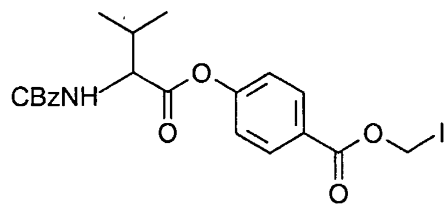
d) Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate.

2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetic acid was esterified by the method described in Example A-I-1, step d. The title compound (1.69 g) was obtained after silica gel column chromatography (0, 1, 2% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.80.

e) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate.
Chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxy)-2-phenyl-DL-acetate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (1.89 g) practically pure. R_f (2%MeOH/$CHCl_3$) 0.80.
^{1}H-NMR ($CDCl_3$): 7.36 (m, 10H), 5.94-5.82 (m, 3H), 5.28 (m, 1H), 5.10 (s, 2H), 4.46 (m, 1H), 2.21 (m, 1H), 1.08-0.85 (m, 6H).

Example A-I-7

Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate.



a) 4-Methoxybenzyl 4-hydroxybenzoate.
4-Hydroxybenzoic acid (1.38 g) was esterified by alkylation with 4-methoxybenzyl chloride by the method described in Example A-I-1, step a. The title compound (2.06 g) was obtained after silica gel column chromatography (0, 1, 2, 3% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.40.

b) 4-Methoxybenzyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate.
4-Methoxybenzyl 4-hydroxybenzoate was acylated with N-benzyloxycarbonyl-L-valine by the method described in Example A-I-1, step b. The title compound (2.71 g) was obtained after silica gel column chromatography (0, 1% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.70.

c) 4-(N-benzyloxycarbonyl-L-valyloxy) benzoic acid.

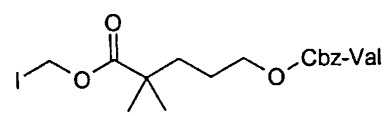
4-Methoxybenzyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate was de-esterified by the method described in Example A-I-1, step c. The title compound (1.86 g) was obtained after silica gel column chromatography (2, 10, 20% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.20. The compound can be activated and esterifed directly to a drug or further modifed as described below.
^{1}H-NMR ($CDCl_3$): 8.15 (d, 2H), 7.34 (m, 5H), 7.22 (d, 2H), 5.38 (d, 1H), 5.17 (s, 2H), 4.58 (d,d, 1H), 2.34 (m, 1H), 1.12 (s, 3H), 0.96 (d, 3H).

d) Chloromethyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate.
4-(N-benzyloxycarbonyl-L-valyloxy) benzoic acid was esterified by the method described in Example A-I-1, step d. The title compound (0.95 g) was obtained after silica gel column chromatography (0, 1% ethanol in dichloromethane). R_f (2%MeOH/$CHCl_3$) 0.80.

e) Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate.
Chloromethyl 4-(N-benzyloxycarbonyl-L-valyloxy) benzoate was converted to iodide by the method described in Example A-I-1, step e to give the title compound (1.16 g) practically pure. R_f (2%MeOH/$CHCl_3$) 0.80.
^{1}H-NMR ($CDCl_3$): 8.11 (d, 2H), 7.35 (m, 5H), 7.21 (d, 2H), 6.15 (s, 2H), 5.32 (d, 1H), 5.14 (s, 2H), 4.55 (d,d, 1H), 2.34 (m, 1H), 1.10 (s, 3H), 1.03 (d, 3H).

Example A-1-8

<u>Iodomethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate</u>



a) 4-Methoxybenzyl 2,2-dimethyl-4-pentenoate
To a solution of 2,2-dimethyl-4-pentenoic acid (11.5 g, 90 mmol) in DMF (250 mL) at room temperature, was added potassium tert-butoxide (11.1 g, 99 mmol). The reaction mixture was stirred at 60 °C for 1h. 4-Methoxybenzyl chloride (16.9 g, 108 mmol) was added and the reaction mixture was stirred at 60 °C for 4h. The DMF was evaporated under vacuum, the residue was dissolved in ether (500 mL) and washed

with water (3 x 200 mL). The organic phase was dried with Na_2SO_4 and evaporated to give 21.4 g of 4-methoxybenzyl 2,2-dimethyl-4-pentenoate.

b) 4-Methoxybenzyl 5-hydroxy-2,2-dimethylvalerate

A mixture of 4-methoxybenzyl 2,2-dimethyl-4-pentenoate (9.50 g, 38 mmol) and 9-BBN (115 mL, 57 mmol, 0.5 M in THF) was stirred at 60 °C for 60 min, whereupon the reaction mixture was cooled to -5 °C. H_2O (35 mL) was added, the reaction mixture was stirred for 5 min at -5 °C, an aqueous solution of NaOH (35 mL, 3M) was added and the reaction mixture was stirred for a further 10 min at -5 °C. An aqueous solution of H_2O_2 (35 mL, 30%) was added dropwise and the temperature of the reaction mixture was allowed to assume room temperature, whereupon the reaction mixture was stirred for 30 min at room temperature. After evaporation, water (200 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (5 x 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 1→8% MeOH in CH_2Cl_2), to give 6.32 g of 4-methoxybenzyl 5-hydroxy-2,2-dimethylvalerate.

c) 4-Methoxybenzyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate

To a mixture of DCC (9.41 g, 46 mmol), DMAP (0.586 g, 4.8 mmol) and N-CBz-L-valine (12.1 g, 48 mmol) in CH_2Cl_2 (200 mL) at 0 °C, was added dropwise a solution of 4-methoxybenzyl 5-hydroxy-2,2-dimethyl-valerate (6.40 g, 24 mmol) in CH_2Cl_2 (50 mL). After 1h at 0 °C, the temperature of the reaction mixture was allowed to assume room temperature and then the mixture was stirred for 5h at room temperature. The mixture was filtered through a glass filter and the solvent was removed under reduced pressure. The crude product was column chromatographed (silica gel, 1→4% MeOH in CH_2Cl_2), to give 8.61 g 4-methoxybenzyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate.

d) 5-(N-CBz-L-valyloxy)-2,2-dimethylvaleric acid

To a solution of 4-methoxybenzyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate (8.24 g, 16.5 mmol) in CH_2Cl_2 (100 mL) at room temperature, was added trifluoroacetic acid (5 mL). After 1h at room temperature, the reaction mixture was concentrated

under reduced pressure. The crude product was column chromatographed (silica gel, 3→5% MeOH in CH_2Cl_2), to give 6.00 g of 5-(N-CBz-L-valyloxy)-2,2-dimethylvaleric acid. The compound can be activated and directly esterified to a drug or further modified as described below.

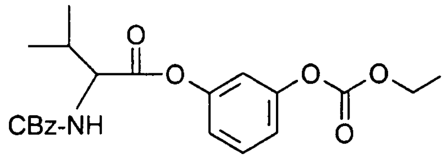
^{1}H-NMR ($CDCl_3$): 10.94 (br s, 1H), 7.35 (s, 5H), 5.45 (d, 1H), 5.11 (s, 2H), 4.30 (dd, 1H), 4.21-4.00 (m, 2H), 2.28-2.07 (m, 1H), 1.68-1.51 (m, 4H), 1.21 (s, 6H), 0.97 (d, 3H), 0.89 (d, 3H).

e) Chloromethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate

To a solution of 5-(N-CBz-L-valyloxy)-2,2-dimethylvaleric acid (5.88 g, 15.5 mmol) in dioxane (100 mL), was added dropwise a 40% aqueous solution of tetrabutylammonium hydroxide (10.1 g). After stirring for 5 min, the solution was evaporated to dryness through co-evaporation with dioxane and toluene. The residue was dissolved in dichloromethane (100 mL) and then chloroiodomethane (11.3 mL, 155 mmol) was added and the solution was stirred for 6h at room temperature. The solution was concentrated under reduced pressure and the residue was shaken with hexane / ethyl acetate (1:1 v/v, 200 mL). The yellow crystalline solid was filtered off and the filtrate was washed with aqueous solution of sodium thiosulfate (0.1 M) and the filtered through anhydrous sodium sulfate and evaporated to dryness. The residue was column chromatographed (silica gel, 1-4% MeOH in CH_2Cl_2), to give 3.95 g of chloromethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate.

f) Iodomethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate.

To a solution of chloromethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate (3.85 g, 9 mmol) in acetonitrile (50 mL), was added sodium iodide (5.40 g, 36 mmol). The solution was stirred for 4 h at 60 °C. The resulting suspension was filtered and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and washed with aqueous sodium thiosulfate (0.1 M). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 1% MeOH in CH_2Cl_2), to give 4.26 g of iodomethyl 5-(N-CBz-L-valyloxy)-2,2-dimethylvalerate



a) 3-(N-CBz-L-valyloxy)phenol.

CBz-L-valine (10 g, 40 mmol), 1,3-dihydroxybenzene (8.7g, 79 mmol) *N,N'*dicychlohexylcarbodiimide (10.2g, 44 mmol) and 4-dimethylaminopyridine (2.4 g, 20 mmol) were dissolved in DMF (50 ml) and left at ambient temperature overnight. The reaction mixture was filtered, the solvent removed under reduced pressure and the crude product was taken up in dichloromethane and filtered. Removal of the solvent followed by purification by chromatography (chloroform-methanol, 10:1) yielded pure title product (10.9 g, 79%).

b) (N-CBZ-L-valyloxy)phenyl chloromethyl carbonate.

3-(N-CBz-L-valyloxy)phenol (5.4 g, 15 7 mmol) was dissolved in dichloromethane (70 ml) and cooled in an ice-bath. Pyridine (1.2 g, 23.5 mmol was added followed by dropwise addition of 1-chloro-methylchloroformate (2.3 g, 18.8 mmol) in dichloromethane (10 ml). The mixture was left at room temperature for 4 h. Water (25 ml) was then added and the phases were separated. The organic layer was washed with 0.01 M aqueous hydrochloric acid (25 ml). Purification by chromatography (ethyl acetate-hexane, 1:1) gave the title compound (4.5 g, 65 %)

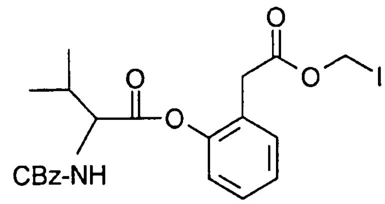
c) 3-(N-CBZ-L-valyloxy)phenyl iodomethyl carbonate

(N-CBZ-L-valyloxy)phenyl chloromethyl carbonate (1.5g, 3.44 mmol) and sodium iodide (2 g, 13.3 mmol) were stirred at 60°C in acetonitrile (50 ml) for 4.5 h.The mixture was filered, the solvent removed and the crude product was taken up in 100 ml hexane-ethyl acetate, 1:1, and filtered through a sintered glass funnel, packed with 2 cm silica gel. Removal of the solvent yielded pure title product (1.68 g, 92%)

^{1}H NMR ($CDCl_3$, 45 °C): 7.38-7.02 (m, 9H), 6.03 (s, 2H), 5.2 (br s, 1H), 5.14 (s, 2H), 4.48 (m, 1H), 2.30 (m, 1H), 1.09-1.01 (m, 6H)

Example A-I-18

Iodomethyl 2-(N-CBZ-L-valyloxy)phenylacetate



a) 4-Methoxybenzyl 2-hydroxyphenylacetate.

2-hydroxyphenylacetic acid (10 g, 66 mmol) was dissolved in *N,N*-dimethylformamide (100 ml) and cooled on ice-bath. Potassium *tert*-butoxide (8.85 g, 78 mmol) was added. The mixture was left for 30 min and allowed to reach room temperature. 4-Methoxy-benzylchloride (11.7 g, 72 mmol) in *N,N*-dimethylformamide (30 ml) was then added dropwise, under nitrogen atmosphere and left over-night. The solvent was evaporated under reduced pressure and the crude mixture was dissolved in ether (100 ml) and washed with water (25 ml), brine and dried over sodium sulphate. Chromatography (hexane-ethyl acetate, 2:1) followed by recrystallization (hexane-ethyl acetate) gave the title compound (7.6 g, 42%).

b) 4-Methoxybenzyl 2-(N-CBz-L-valyloxy)phenylacetate

4-Methoxybenzyl 2-hydroxyphenylacetate 3g, 11 mmol), *N,N,*-dichyclohexylcarbodiimide (2.7 g, 13.2 mmol), dimethylaminopyridine (0.134 g, 1.1 mmol) and CBz-L-valine (3.3 g, 13.2 mmol) were dissolved in dichloromethane (50 ml). After the weekend the solid was filtered off, the solvent removed under reduced pressure and the crude product purified by chromatography (ethyl acetate, hexane, 1:2) to give the title compound (5.2 g, 93%).

c) 2-(N-CBz-L-valyloxy)phenylacetic acid

4-Methoxybenzyl 2-(N-CBz-L-valyloxy)phenylacetate (4.25 g, 8.4 mmol), was dissolved in dichloromethane (40 ml). Triflouroacetic acid (8 ml) was added with cooling on ice. The mixture was allowed to reach room temperature and stirred for 40 min. The solvent was removed under reduced pressure and the crude product was recrystallized twice (hexan-ethyl acetate + a small amount of dichloromethane) to give the title compound (2.6 g, 80 %). The compound can be activated and esterified to a drug or further modified as described below.

^1H NMR ($CDCl_3$, 45 °C): 7.35-7.08 (m, 9H), 5.35 (br s, 1H), 5.13 (s, 2H), 4.48 (m, 1H), 3.57 (s, 2H), 2.33 (m, 1H), 1.08 (d, 3H), 1.02 (d, 3H).

d) Chloromethyl 2-(N-CBZ-L-valyloxy)phenylacetate

This compound was prepared in poor yield from 2-(N-CBz-L-valyloxy)phenylacetic acid (5.5 g, 14.3 mmol) by an unoptimized procedure essentially as described in Example A-I-16 d). Yield: 0.265 g

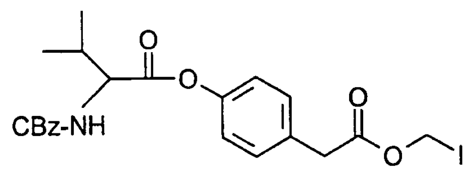
^1H NMR ($CDCl_3$ 45 °C): 7.28-7.01 (m, 9H), 5.55 (s, 2H), 5.2 (br s, 1H), 5.07 (s, 2H), 4.43 (m, 1H), 3.53 (s, 2H), 2.26 (m, 1H), 1.02 (d, 3H), 0.95 (d, 3H).

e) Iodomethyl 2-(N-CBZ-L-valyloxy)phenylacetate

Chloromethyl 2-(N-CBZ-L-valyloxy)phenylacetate is treated with NaI and purified as described in the Examples above to yield the title compound.

Example A-I-19

Iodomethyl 4-(N-CBZ-L-valyloxyxy)phenylacetate



a) 4-Methoxybenzyl 4-hydroxyphenylacetate

Prepared from 4-hydroxyphenylacetic acid (10 g, 65.7 mmol) in 70 % yield by the same procedure as for Example A-I-18 a) above, but wherein the solvent for the recrystallization was changed to hexane-ether.

b) 4-Methoxybenzyl 4-(N-CBz-L-valyloxy)phenylacetate

Prepared from 4-methoxybenzyl 4-hydroxyphenylacetate (3 g, 11 mmol) by the same procedure as for Example A-I-18 b) in 87 % yield. Solvent for chromatography: ethyl acetate-hexane, 1:2.

c) 4-(N-CBZ-L-valyloxy)phenylacetic acid

Prepared in 82 % yield from 4-methoxybenzyl 4-(N-CBz-L-valyloxy)phenylacetate (1.6 g, 288 mmol) by the procedure described for Example A-I-18 c). Solvent for recrystallization: hexane-ether and a small amount of dichloromethane. The compound can be activated and esterified to a drug or further modified as described below.

^{1}H NMR ($CDCl_3$ 45 °C): 7.36-7.27 (m, 7H), 7.02 (d, 2H), 5.25 (d, 1H), 5.14 (s, 2H), 4.52 (m, 1H), 3.64 (s, 2H), 2.3 (m, 1H), 1.08 (d, 3H), 1.02 (d, 3H).

d) Chloromethyl 4-(N-CBZ-L-valyloxy)phenylacetate

Prepared from 4-(N-CBZ-L-valyloxy)phenylacetic acid (3 g, 7.8 mmol) in 26 % yield by the same procedure as described for Example A-I-18 d). Solvent for chromatography: hexane-ether, 3:2.

e) Iodomethyl 4-(N-CBZ-L-valyloxy)phenylacetate

Chloromethyl 4-(N-CBZ-L-valyloxy)phenylacetate (0.83 g, 1.9 mmol) and sodium iodide (1.15 g, 7.6 mmol) were heated in acetonitril (45 ml) for 5 h. The mixture was filtrated, the solvent removed, taken up in dichloromethane and filtrated again. Evaporation and purification by chromatography (ether-hexane, 2:3) yielded the title product (0.8 g, 80 %).

^{1}H NMR ($CDCl_3$ 45 °C): 7.38-7.09 (m, 4H), 5.84 (s, 1H), 5.30 (br s, 1H), 5.15 (s, 2H), 4.5 (m, 1H), 3.56 (s, 2H), 2.36 (m, 1H), 1.10 (d, 3H), 1.00 (d, 3H).

Example A-I-20

Iodomethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl) benzoate

a) 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)–toluene

To a cooled solution of 4-methylphenylethanol-2 (5.0g, 36.7 mmole), 4-dimethylaminopyridine (0.98g, 8 mmole) and N-benzyloxycarbonyl-L-valine (10.05g, 40 mmole) in dichloromethane (120 ml) was added dicyclohexyl-carbodiimide (9.1g, 44 mmole) and the mixture was stirred overnight at room

temperature. The mixture was cooled and the urethane was filtered. The solution was evaporated under reduced pressure and ethyl acetate (250 ml) was added. The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography

b) 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)- benzoic acid .

To a cooled mixture of chromic anhydride (7.55g, 75 mmole) in acetic acid (100 ml) was added dropwise a solution of 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)-toluene (9.3g, 25.1 mmole) in acetone (50 ml). The mixture was stirred at room temperature for 3 days and reduced to about 100 ml. 600ml 10% sodium chloride solution was added and the mixture was extracted four times with ethyl acetate. The organic phase was washed with brine and dried with sodium sulfate. The solution was evaporated under reduced pressure and the product was islolated by silica gel column chromatography with dichloromethane/methanol. Yield : 2,1g = 21%. The product can be activated and esterified directly onto a drug or further modified as described below.^{1}H-NMR ($CDCl_3$) 0.79 (d, 3H) 0.90 (d, 3H) 2.08 (m,1H) 3.04 (t, 2H) 4.28 (d, d,1H)4.39 (m, 2H) 5.11 (s, 2H) 5.26 (d, 1H) 7.34 (m, 7H) 8.04 (d, 2H)

c) Chloromethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)benzoate

To a solution of 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)benzoic acid (2.0g, 5.0 mmole) in 1,4-dioxane (20 ml)was added a 40% solution of tetrabutylammonium hydroxide (3.1g, 4.75 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and coevaporated two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in dichloromethane (10 ml) and iodochloromethane (13.2g, 75 mmole) was added The solution was stirred overnight at room temperature and evaporated under reduced pressure. About 50 ml ethyl acetate were added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography.Yield: 0.5g =23%

d) Iodomethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl) benzoate

To a solution of chloromethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethyl) benzoate (0.5g, 1.11 mmole). In dry acetone (10 ml) was added sodium iodide (0.75g, 5.0 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl actate/water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure.Yield: 0.53g = 88%.

^{1}H-NMR ($CDCl_3$) 0.88 (d, 3H) 0.90 (d, 3H) 2.08 (m, 1H) 3.02 (t, 2H) 4.28 (d, d, 1H) 4.38 (m, 2H) 5.10 (s, 2H) 5.22 (d, 1H) 6.15 (s, 2H) 7.35(m, 7H) 7.98 (d, 2H)

Example A-I-21

Iodomethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl) 2-methyl propionate.

a) 4-methoxybenzyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl propionate

To a cooled solution of 4-methoxybenzyl 2-(hydroxymethyl)-2-methyl propionate (6.0g, 25 mmole), 4-dimethylaminopyridine (0.61g, 5 mmole) and N-benzyloxycarbonyl-L-isoleucine (6.90g, 26 mmole) in dichloromethane (100 ml) was added dicyclohexyl-carbodiimide (6.2g, 30 mmole) and the mixture was stirred overnight at room temperature.The mixture was cooled and the urethane was filtered. The solution was evaporated and 200 ml ethyl acetate was added, The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone.Yield: 11.7g = 96%.

2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl) propionic acid.

To a solution of 4-methoxybenzyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl propionate (11.0g, 22.6 mmole) in 100 ml dichloromethane was added trifluoroacetic acid (15 ml) and the mixture was stirred overnight at room temperature. The solution was evaporated under reduced pressure and coevaporated two times with toluene. The residue was stirred 1 hour with 100 ml ethanol and the white solid was filtered (byproduct). The solution was evaporated under reduced

pressure and the product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 7.4g = 89%. The product can be activated and esterified directly to a drug, or further modified as described below.

^{1}H-NMR ($CDCl_3$) 0.90 (m, 6H) 1.26 (m, 8H) 1.88 (m, 1H) 4.12 (d, d, 2H) 4.38 (d, d, 1H) 5.10 (s, 2H) 5.32 (d, 1H) 7.28 (m, 5H)

c) Chloromethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxy)-2-methyl propionate.

To a solution of 2-(N-benzyloxycarbony-L-isoleucyloxymethyl)-2-methyl propionic acid (7.0g, 19 mmole) in 80 ml 1,4-dioxane was added a 40% solution of tetrabutylammonium hydroxide (12.4g, 19 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in 25 ml dichloromethane and iodochloromethane (33.7g, 190 mmole) was added . The solution was stirred overnight at room temperature and evaporated under reduced pressure. About 100 ml ethyl actate was added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone.Yield: 4.2 = 54%

d) Iodomethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl propionate.

To a solution of chloromethyl 2-(N-benzyloxycarbonyl-L-isoleucyloxymethyl)-2-methyl propionate (3.0g, 7.2 mmole) in 50 ml dry acetone was added sodium iodide (4.8g, 32 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl actate water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield: 3.3g = 90%.

^{1}H-NMR ($CDCl_3$) 0.93 (m, 6H) 1.23 (m, 8H) 4.12 (m, 2H) 4.38 (d, d, 1H) 5.10 (s, 2H) 5.26 (d, 1H) 5.92 (m, 2H) 5.35 (m, 5H)

Example A-I-22

Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy)cyclohexanoate.

a) 4-Methoxybenzyl 4-hydroxycyclohexanoate.

To a solution of ethyl 4-hydroxycyclohexanoate (8.61g, 50 mmole) in 50 ml ethanol was added a solution of potassium hydroxide 85% (3.63g, 55 mmole) and the mixture was stirred for 6 hours at 70°C. The mixture was evaporated under reduced pressure, coevaporated two times with N,N-dimethylformamide and reduced to about 100 ml. 4-Methoxybenzyl chloride (9.4g, 60 mmole) was added and the mixture was stirred for 18 hours at 60°C. The mixture was evaporated under reduced pressure and 250 ml ethyl acetate was added. The organic phase was washed five times with water, dried with sodiun sulfate and evaporated under reduced pressure. Yield: 13.2g =100% (crude)

b) 4-methoxybenzyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate.

To a cooled solution of 4-methoxybenzyl 4-hydroxycyclohexanoate (7.5g, 28 mmole), 4-dimethylaminopyridine (0.73g, 6 mmole) and N-benzyloxycarbonyl-L-valine (7.54g, 30 mmole) in dichloromethane (90 ml) was added dicylohexyl-carbodiimide (6.8g, 33 mmole) and the mixture was stirred for 2 days at room temperature. The mixture was cooled and the urethane was filtered. The solution was evaporated and 250 ml ethyl acetate was added.The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone.Yield : 13g = 93%

c) 4-(N-benzyloxycarbonyl-L-valyloxy) cyclohexanoic acid.

To a solution of 4-methoxybenzyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate (12g, 24.1 mmole) in dichloromethane (100 ml) was added trifluoroacetic acid (20 ml) and the mixture was stirred for 3 hours at room temperature. The solution was evaporated under reduced pressure and coevaporated two times with toluene. The residue was stirred 1 hour with about 100 ml ethanol and the white solid was filtered (byproduct). The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography with

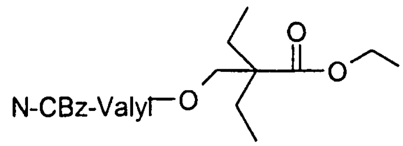
toluene/acetone. Yield: 6.8g = 74%. The product can be activated and esterified directly to a drug or further modified as described below.
^{1}H-NMR ($CDCl_3$) 0.91 (m, 6H) 1.52-2.54 (m, 10H) 4.28 (m, 1H) 4.82-5.08 (m, 1H) 5.11 (s, 2H) 5.28 (d, 1H) 7.36 (m, 5H)

d) Chloromethyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate.
To a solution of 4-(N-benzyloxycarbonyl-L-valyloxy) cyclohexanoic acid (6.6g, 20 mmole) in 1,4-dioxane (70 ml) was added a 40% solution of tetrabutylammonium hydroxide (11.34g, 17.5 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in 60 ml dichloromethane and iodochloromethane (30.9g, 175 mmole) was added. The solution was stirred for two days at room temperature and evaporated under reduced pressure. About 100 ml ethyl actate was added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with toluene/acetone. Yield: 4.1g = 55%.

e) Iodomethyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate.
To a solution of chloromethyl 4-(N-benzyloxycarbonyl-L-valyloxy)-cyclohexanoate (4.0g, 9.4 mmole) in dry acetone (50 ml) was added sodium iodide (6.3g, 42 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl actate water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure.Yield 4.5g = 93%.
^{1}H-NMR ($CDCl_3$) 0.90 (m, 6H) 1.52-2.02 (m, 8H) 2.18 (m, 1H) 2.43 (m, 1H) 4.30 (m, 1H) 4.76-5.08 (m, 1H) 5.11 (s, 2H) 5.26 (d, 1H) 5.91 (d, 2H) 7.34 (m, 5H)

Example A-I-23

Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyrate



a) 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethylbutan-1-ol.

To a cooled solution of 2-ethyl-2-hydroxymethyl-butan-1-ol (33.1g, 250 mmole), 4-dimethylaminopyridine (1.22g, 10 mmole) and N-benzyloxycarbonyl-L-valine (12.6g, 50 mmole) in 350 ml dichloromethane was added dropwise a solution of dicyclohexyl-carbodiimide (12.4g, 60 mmole) in 50 ml dichloromethane. The mixture was stirred 2 days at room temperature and cooled. The urethane was filtered and the solution evaporated under reduced pressure. 350 ml ethyl acetate was added and the organic phase was washed twice with 5% acetic acid, 5% sodium-hydrogencarbonate and water. The organic phase was dried with sodium sulfat and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with dichloromethane/methanol. Yield: 16.4g = 90%.

c) 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl-butyric acid.

To a cooled mixture of chromic anhydride (8.5g, 85,2 mmole) in 100 ml acetic acid was added dropwise a solution of 2-(N-benzyloxycarbonyl-L-valyoxymethyl)-2-ethyl-butan-1-ol (10.4g, 28.4 mmole) in 50 ml acetone and the mixture was stirred 24 hours at room temperature. The mixture was added to1000 ml 10% sodium chloride solution and extracted four times with ethyl acetate. The organic phase was washed twice with brine, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 7g = 65%. The product can be activated and esterified directly to a drug or futher modified as described below.

^{1}H-NMR ($CDCl_3$) 0.88 (m, 12H) 1.67 (m, 4H) 2.14 (m, 1H) 4.26 (m, 3H) 5.10 (s, 2H) 5.30 (d, 2H) 7.34 (m, 5H)

d) Chloromethyl 2-(N-benzyoxycarbonyl-L-valyloxymethyl –2-ethyl butyrate.

To a solution of 2-(N-benzyloxycarbony-L-valyloxymethyl)–2-ethyl-butyric acid (7.2g,18,9 mmole) in 1,4-dioxane (80 ml) was added a 40% solution of tetrabutylammonium hydroxide (12.26g, 18.9 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated once with 1,4-dioxane and two times with toluene. The dried product was dissolved in 30 ml dichloromethane and iodochloromethane (49.4g, 280 mmole) was added. The solution was stirred for two days at room temperature and evaporated under reduced pressure. About 100 ml ethyl actate were added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 5.2g = 63%

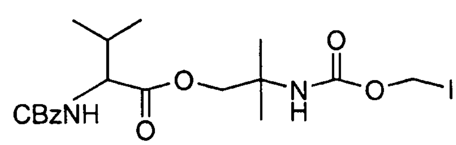
e) Iodomethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyrate.

To a solution of chloromethyl 2-(N-benzyloxycarbonyl-L-valyloxymethyl)-2-ethyl butyrate (5.0g, 11.7 mmole) in dry acetone (60 ml) was added sodium iodide (7.5g, 50 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl actate water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield: 5.4g = 90%.

^{1}H-NMR ($CDCl_3$) 0.92 (m, 12H) 1.65 (m, 4H) 2.18 (m, 1H) 4.28 (m, 3H) 5.10 (s, 2H) 5.22 (d, 1H) 5.92 (s, 2H) 7.36 (m, 5H)

Example A-I-24

2-(N-(iodomethoxycarbonyl)-amino) –2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane



a) 2-(N-tert.-butyloxycarbonylamino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)–propane.

To a cooled solution of 2-(N-(tert.-butyloxycarbonyl)-amino)-2-methylpropan-1-ol (J. Am. Chem. Soc 113 (1991) p 8883) (4.73g, 25 mmole), 4-dimethylamino-

pyridine (0.61g, 5 mmole) and N-benzyloxycarbonyl-L-valine (6.28g, 25 mmole) in dichloromethane (70 ml) was added dicyclohexyl-carbodiimide (6.19g, 30 mmole) and the mixture was stirred 2 days at roommtemperature. The mixture was cooled, the urethane was filtered and the solution evaporated under reduced pressure. Ethyl acetate (200 ml) was added and the organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with,sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate.Yield: 10.2g = 96%.

b) 2-amino-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane.
To a solution of 2-(N-(tert.-butyloxycarbonyl)-amino)–2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane (10g, 23 mmole) in dichloromethane (150 ml) was added trifluoroacetic acid (30 ml) and the mixture was stirred for 1 hour at room temperature. The solution was evaporated under reduced pressure and 10% sodium carbonate solution was added. The product was extracted four times with dichloromethane, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with dichloromethane/methanol. Yield: 3.0g = 40% (crude)

c) 2-(N-(chloromethoxycarbonyl)-amino)-2-methyl-1- (N-benzyloxycarbonyl-L-valyloxy)-propane.
To a solution of 2-amino-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane (2.9g, 9 mmole) and pyridine (2 ml) in dichloromethane (50 ml) was added chloromethyl chloroformate(1.55g, 12 mmole) and the mixture was stirred for 3 hours at room temperature. The mixture was evaporated under reduced pressure and ethyl acetate was added. The organic phase was washed with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with hexane/ethyl acetate.Yield: 1.1g = 29%.

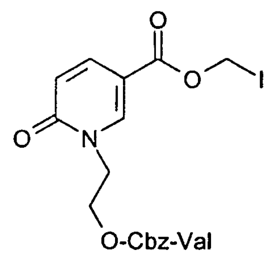
d) 2-(N-(iodomethoxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)-propane.
To a solution of 2-(N-(chloromethoxycarbonyl)-amino)-2-methyl-1-(N-benzyloxycarbonyl-L-valyloxy)propane (1.05g, 2.53 mmole) in dry acetone (20 ml)

was added sodium iodide (1.8g, 12 mmole) and the mixture was stirred for 36 hours at room temperature. The mixture was evaporated under reduced pressure and ethyl acetate and water were added. The organic phase was washed with 10% sodium thiosulfate solution and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure.Yield: 1.04g = 81%.

^{1}H-NMR ($CDCl_3$) 0.92 (m, 6H) 1.35 (s, 6H) 2.10 (m,1H) 3.88 (m, 1H) 4.35 (m, 2H) 5.11 (s, 2H) 5.32 (d, 1H) 5.82 (s, 1H) 5.91 (s, 2H) 7.35 (m, 5H)

Example A-I-25

1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester



a) 6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

To a solution of 6-hydroxynicotinic acid (4.87 g, 35 mmol) in DMF (100 mL) at room temperature, was added potassium tert-butoxide (3.93 g, 35 mmol). The reaction mixture was stirred at 60 °C for 1h. 4-Methoxybenzylchloride (8.30 g, 53 mmol) was added and the reaction mixture was stirred at 60 °C for 4h. The DMF was evaporated under vacuum, the residue was dissolved in ether (200 mL) and washed with water (3 x 100 mL). The organic phase was dried with Na_2SO_4 and evaporated to give 4.41 g of 6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

b) 1-(2-Hydroxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester

To a solution of 6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester (4.41 g, 17 mmol) and K_2CO_3 (2.58 g, 18.7 mmol) in DMF (100 mL) at room temperature, was added 2-bromoethanol (2.02 g, 16.2 mmol). The reaction mixture was stirred at 80 °C for 30h, whereupon the DMF was evaporated under vacuum.

The crude product was column chromatographed (silica gel, 2→5% MeOH in CH_2Cl_2), to give 3.91 g of 1-(2-hydroxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

c) 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester

To a mixture of DCC (5.06 g, 24.5 mmol), DMAP (318 mg, 2.6 mmol) and N-CBz-L-valine (6.48 g, 25.8 mmol) in CH_2Cl_2 (200 mL) at 0 °C, was added dropwise a solution of 1-(2-hydroxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester (6.40 g, 24 mmol) in CH_2Cl_2 (200 mL). After 1h at 0 °C, the temperature of the reaction mixture was allowed to assume room temperature and then the mixture was stirred for 5h at room temperature. The mixture was filtered through a glass filter and the solvent was removed under reduced pressure. The crude product was column chromatographed (silica gel, 2→5% MeOH in CH_2Cl_2), to give 6.81 g 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester.

d) 1-(2-N-CBz-L-valyloxyethyl)-2-pyridone-5-carboxylic acid

To a solution of 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 4-methoxybenzyl ester (6.46 g, 12 mmol) in CH_2Cl_2 (85 mL) at room temperature, was added trifluoroacetic acid (15 mL). After 1h at room temperature, the reaction mixture was concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 3→6% MeOH in CH_2Cl_2), to give 4.91 g 1-(2-N-CBz-L-valyloxyethyl)-2-pyridone-5-carboxylic acid. The product can be activated and esterified direct to a drug or further modified as described below.

^{1}H-NMR ($CDCl_3$): 12.15 (br s, 1H), 8.29 (d, J = 2.2 Hz, 1H), 7.93 (dd, J = 9.5, 2.2 Hz, 1H), 7.31 (m, 5H), 6.69 (d, J = 9.5 Hz, 1H), 5.53 (d, 1H), 5.07 (s, 2H), 4.52-4.05 (m, 5H), 2.20-2.00 (m, 1H), 0.90 (d, 3H), 0.81 (d, 3H).

e) 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid chloromethyl ester

To a solution of 1-(2-N-CBz-L-valyloxyethyl)-2-pyridone-5-carboxylic acid (4.91 g, 11.8 mmol) in dioxane (200 mL), was added dropwise a 40% aqueous solution of tetrabutylammonium hydroxide (7.65 g). After stirring for 5 min, the solution was evaporated to dryness through co-evaporation with dioxane and toluene. The residue was dissolved in dichloromethane (200 mL) and then chloroiodomethane (8.74 mL, 120 mmol) was added and the solution was stirred for 12h at room temperature. The solution was concentrated under reduced pressure and the residue was shaken with hexane / ethyl acetate (1:1 v/v, 200 mL). The yellow crystalline solid was filtered off and the filtrate was washed with aqueous solution of sodium thiosulfate (0.1 M) and the filtered through anhydrous sodium sulfate and evaporated to dryness. The residue was column chromatographed (silica gel, 2-4% MeOH in CH_2Cl_2), to give 1.80 g of 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid chloromethyl ester.

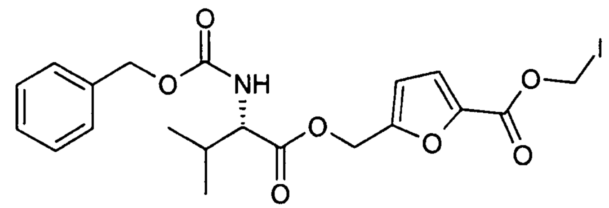
f) 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester

To a solution of 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid chloromethyl ester (1.80 g, 3.87 mmol) in acetonitrile (30 mL), was added sodium iodide (2.32 g, 15.5 mmol). The solution was stirred for 4 h at 60 °C. The resulting suspension was filtered and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and washed with aqueous sodium thiosulfate (0.1 M). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was column chromatographed (silica gel, 1% MeOH in CH_2Cl_2), to give 2.04 g 1-(2-N-CBz-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester.

^{1}H-NMR ($CDCl_3$): 8.19 (d, J = 2.5 Hz, 1H), 7.79 (dd, J = 9.6, 2.5 Hz, 1H), 7.32 (m, 5H), 6.52 (d, J = 9.6 Hz, 1H), 6.04 (s, 2H), 5.38 (d, 1H), 5.07 (s, 2H), 4.54-4.06 (m, 5H), 2.20-2.00 (m, 1H), 0.91 (d, 3H), 0.81 (d, 3H).

Example A-I-26

Iodomethyl 5-[(*N*-benzyloxycarbonyl-L-valyloxy)methyl]-2-furoate



(a) 5-[(*N*-Benzyloxycarbonyl-L-valyloxy)methyl]-2-furaldehyde

A solution of 5-(hydroxymethyl)-2-furaldehyde (1.00 g, 7.69 mmol) in 5 mL dry CH_2Cl_2 was added to a mixture of *N*-benzyloxycarbonyl-L-valine (2.40 g, 9.57 mmol), *N,N'*-dicyclohexylcarbodiimide (2.00 g, 9.69 mmol), and 4-dimethyl-aminopyridine (117 mg, 0.96 mmol) in 45 mL CH_2Cl_2. After stirring overnight, the reaction slurry was filtered, concentrated under vacuum, and subjected to flash column chromatography (silica, 2/1 petroleum ether - ethyl acetate to give the valine ester (quantitative yield).

(b) 5-[(*N*-Benzyloxycarbonyl-L-valyloxy)methyl]-2-furoic acid

A solution of $NaClO_2$ (2.8 mmol) in 3 mL water was added dropwise to a stirred solution of 5-[(*N*-benzyloxycarbonyl-L-valyloxy)methyl]-2-furaldehyde (798 mg, 2.22 mmol) from step (a) in 3 mL MeCN, with cooling in an ice bath. After 2.5 h, the ice bath was removed, 2 mL more MeCN was added, and the two-phase liquid reaction mixture was stirred at room temperature for 25 h. The reaction mixture was diluted with water, made basic with saturated $NaHCO_3$, and extracted with ethyl acetate (3 x 50 mL). The separated aqueous solution was acidified to pH 2 with 5% aqueous HCl and extracted with ethyl acetate (3 x 50 mL). This second ethyl acetate solution was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness under vacuum to give the carboxylic acid (287 mg, 34%) which was used in the next step without further purification. The compound can be activated and esterified direct to a drug or further modified as described below.

^1H NMR (250 MHz, $CDCl_3$) δ 0.84 and 0.93 (2d, 3H each, J = 6.8 Hz), 2.15 (m, 1H), 4.35 (dd, 1H, J = 9.0, 4.7 Hz), 5.10-5.24 (m, 4H), 5.44 (d, 1H, J = 9.0 Hz), 6.54 (d, 1H, J = 3.3 Hz), 7.23 (d, 1H, J = 3.3 Hz), 7.33 (s, 5H), 11.05 (br s, 1H).

(c) Chloromethyl 5-[(*N*-benzyloxycarbonyl-L-valyloxy)methyl]-2-furoate

Tetrabutylammonium hydroxide (40 wt. % solution in water, 0.55 mL, 0.84 mmol) was added to the carboxylic acid (286 mg, 0.76 mmol) from step (b) in 5 mL dioxane. The yellow solution was concentrated under vacuum, coevaporating several times with dioxane, toluene, and, lastly, CH_2Cl_2. The residue was charged with 10 mL dry CH_2Cl_2 and chloroiodomethane (0.55 mL, 7.55 mmol) was added. After stirring for 20.5 h, the reaction mixture was concentrated and subjected to flash column chromatography (silica, 2/1 petroleum ether - ethyl acetate) to give the chloromethyl ester (137 mg, 42%).

(d) Iodomethyl 5-[(*N*-benzyloxycarbonyl-L-valyloxy)methyl]-2-furoate

All of the chloromethyl ester (137 mg, 0.32 mmol) from step (c) was refluxed with NaI (195 mg, 1.3 mmol) in 3.2 mL dry MeCN at 70 °C for 4 h. The solvent was removed under vacuum and the residue was subjected to flash column chromatography (silica, 3/1 petroleum ether - ethyl acetate) to give the iodomethyl ester (152 mg, 92%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 0.84 and 0.93 (2d, 3H each, J = 6.8 Hz), 2.16 (m, 1H), 4.33 (dd, 1H, J = 9.1, 4.7 Hz), 5.09-5.21 (m, 4H), 5.36 (d, 1H, J = 9.1 Hz), 6.08 (s, 2H), 6.52 (d, 1H, J = 3.4 Hz), 7.19 (d, 1H, J = 3.5 Hz), 7.33 (s, 5H).

Example A-I-27

4-(2-N-benzyloxycarbonyl-L-valyloxyethyl)benzoic acid .

a) 4-Methoxybenzyl 4-(2-hydroxyethoxy)benzoate

To a solution of 4-methoxybenzyl 4-hydroxybenzoate (7.0g, 27 mmole) in dry N,N-dimethylformamide (50 ml) was added potassium carbonate (4.15g, 30 mmole) and 2-bromoethanol.The mixture was stirred 48 hours at 80°C, evaporated under reduced pressure and ethyl acetate and water were added. The organic phase was washed five times with water and dried with sodium sulfate. The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography with hexane/ethyl acetate. Yield: 6.8g = 83%.

b) 4-methoxybenzyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy)benzoate.

To a solution of 4-methoxybenzyl 4-(2-hydroxyethoxy) benzoate (6.6g, 21.8 mmole), 4-dimethylaminopyridine (0.61g, 5 mmole) and N-benzyloxycarbonyl-L-valine (6.3g, 25 mmole) in dichloromethane (80 ml) was added dicyclohexyl-carbodiimide (5.2g, 25 mmole) and the mixture was stirred overnight at room temperature. The mixture was cooled and the urethane was filtered.The solution was evaporated and ethyl acetate (200 ml) was added. The organic phase was washed twice with 5% acetic acid, 5% sodium hydrogencarbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography with dichloromethane/methanol. Yield: 10.6g = 90 %.

c) 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy)-benzoic acid.

To a solution of 4-methoxybenzyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy) benzoate (10.2g, 19.04 mmole) in dichloromethane (100 ml) was added trifluoroacetic acid (20 ml) and the mixture was stirred 3 hours at room temperature. The solution was evaporated under reduced pressure and co-evaporated two times with toluene. The product was isolated by silica gel column chromatography. Yield: 6.9g = 87%. The product may be activated and esterified direct to a drug or converted to iodomethyl 4-(2-N-benzyloxycarbonyl-L-valyloxyethoxy)-benzoic acid as described above, that is by treatment with a base, chloroiodomethane, separation and then treatment with NaI.

^{1}H-NMR ($CDCl_3$) 0.94 (m, 6H) 2.18 (m, 1H) 4.22- 4.68 (m, 5H) 5.10 (s, 2H) 6.94 (d, 2H) 7.35 (m, 5H) 8.05 (d, 2H)

Example 1

3,3-Bis (N-CBZ-L-valyloxymethyl)-propionic acid

a) 4,4-bis (N-CBZ-L-valyloxymethyl)-but-1-ene.

To a solution of 2-allyl-1,3-propandiol (2.32g, 20 mmole), N-CBZ-L-valine (10.06g, 40 mmole) and DMAP (0.488g, 4 mmole) in 120ml dichloromethane was added DCC (9.08g, 44 mmole) in portions and the mixture was stirred overnight at room temperature. The mixture was cooled to 5°C and the urethane was filtered. The

filtrate was evaporated and the product was isolated by silica gel column chromatography. Yield : 9.0g

b) 3,3-Bis (N-CBZ-L-valyloxymethyl)-propionic acid.

To a cooled solution of 4,4-bis (N-CBZ-L-valyloxymethyl)-but-1-ene (14.6g, 25 mmole) and tetrabutylammonium bromide (1.3g, 4 mmole) in 120ml benzene was added 100ml water. Under strong stirring potassium permanganate (15.8g, 100 mmole) was addded in portions and the mixture was stirred for 2 hours between 15°C and 20°C . A sodium bisulfite aqueous solution was added to the slurry until the mixture was discolored. The mixture was acidified with 2N hydrochloric acid and extracted four times with ethyl acetate. The organic phase was washed two times with water, dried with sodium sulfate and evaporated under reduced pressure . The product was isolated by silica gel column chromatography. Yield: 7.5g

^{1}H-NMR ($CDCl_3$) 0.89 (m, 12H) 2.05 (m, 2H) 2.46 (m, 2H) 2.62 (m, 1H) 4.20 (m, 6H) 5.11 (s, 4H) 5.30 (m, 2H) 7.35 (m, 10H)

Example 2

2', 3'-Dideoxy-3'-fluoro-5'-O- [3,3-bis (L-valyloxymethyl)-propionyl] guanosine

a) 2',3'-dideoxy-3'-fluoro-5'-O-[3,3-bis (N-CBZ-L-valyloxymethyl)-propionyl]guanosine.

A solution of 2',3'-dideoxy-3'-fluoroguanosine (1.35g, 5 mmole), 3,3-bis (N-CBZ-L-valyloxymethyl)-propionic acid (3.6g, 6 mmole), DMAP (0.061g, 0.5 mmole) and HOBT (0.81g, 6 mmole) was coevaporated two times with DMF and reduced to about 120ml. DCC (1.24g, 6 mmole) was added and the mixture was stirred overnight at room temperature. The mixture was filtered and the solution was evaporated under reduced pressure. Ethyl acetate (200 ml) was added and the organic phase washed twice with 5% acetic acid, 5% sodium hydrogen carbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 2.7g

d) 2', 3'-Dideoxy-3'-fluoro-5'-O- [3,3-bis (L-valyloxymethyl)-propionicacid] guanosine.

A solution of 2', 3'-dideoxy-3'-fluoro-5'-O-[3,3-bis (N-CBZ-L-valyloxymethyl)-propionyl] guanosine (2.6g, 3.1 mmole) in 80ml ethyl acetate, 20ml methanol and 20ml acetic acid was hydrogenated with palladium black (0.3g) for two hours under normal pressure. The catalyst was filtered and washed with ethyl acetate and methanol. The solution was evaporated under reduced pressure and the product was isolated as the bisacetate salt by silica gel column chromatography. Yield: 1.2g
^{1}H-NMR (DMSO d-6) 0.90 (m, 12H) 1.78 (m, 2H) 2.50-3.00 (m, 2H) 3.09 (m, 2H) 4.02-4.45 (m, 8H) 5.34-5.59 (m, 1H) 6.17 (m, 1H) 6.62 (s, 2H) 7.88 (s, 1H)

Example 3

2', 3'-Dideoxy-3'-fluoro-5'-O-3-[1,3-bis-(L-valyloxy)-2-propyloxycarbonyl propanoyl]guanosine

a) 1,3-dibenzyloxy-2-propyl succinate monoester.

A solution of 1,3-dibenzyloxypropan-2-ol (6.8g, 25 mmole) and succinic anhydride (7.5g, 75 mmole) and DMAP (12.2g, 100 mmole) was stirred for one hour at 60°C. The mixture was evaporated under reduced pressure, acidified with 2N HCl and extracted two times with ethyl actate. The combined organic phase was washed three times with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 7.8g

b) Synthesis of 2', 3'-dideoxy-3'-fluoro-5'-O-[3-(1,3-dibenzyloxy-2-propyloxycarbonyl)-propanoyl] guanosine.

A mixture of 2', 3'-dideoxy-3'-fluoroguanosine (1.61g, 6 mmole), HOBT (0.972g, 7.2 mmole), DMAP (73.3mg, 0.6 mmole) and 1,3-dibenzyloxy-2-propyl succinate monoester (2.68g, 7,2 mmole) was coevaporated two times with DMF and reduced to about 150ml. DCC (1.55g, 7.5 mmole) was added and the mixture was stirred 72 hours at room temperature. The mixture was filtered and the solution was evaporated under reduced pressure. Ethyl acetate (200 ml) was added and the organic phase washed twice with 5% acetic acid, 5% sodium hydrogen carbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 3.3g

c) Synthesis of 2', 3'-dideoxy-3'-fluoro-5'-O [3-(1,3-dihydoxy-2-propyloxy carbonyl)propanoyl]guanosine.

A solution of 2', 3'-dideoxy-3'-fluoro-5'-O-[3-(1,3-dibenzyloxy-2-propyloxy carbonyl)propanoyl]guanosine (3.2g, 5.13 mmole) in 50ml ethyl acetate, 50ml methanol and 10ml acetic acid was hydrogenated with palladium black (0.6g) under 40 psi overnight. The catalyst was filtered and washed with methanol, The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromathography. Yield: 1.64g

d) Synthesis of 2',3'-dideoxy-3'-fluoro-5'-O- {3-[1,3-Bis (N-CBZ-L-valyloxy)-2-propyloxycarbonyl]propanoyl} guanosine.

A mixture of 2',3'-dideoxy-3'-fluoro-5'-O-[3-(1,3-dihydroxy-2-propyloxy carbonyl)-propanoyl]guanosine (1.93g, 2.93 mmole), N-CBZ-L-valine (1.76g, 7 mmole), HOBT (0.95g, 7 mmole) and DMAP (85.5mg, 0.7 mmole) was coevaporated two times with DMF and reduced to about 60ml. DCC (1.55g, 7.5 mmole) was added and the mixture was stirred overnight at room temperature. The mixture was warmed for four hours at 60°C and then cooled to about 10°C. The mixture was filtered and the solution was reduced under reduced pressure. Ethyl acetate (150 ml) was added and the organic phase was washed twice with 5% acetic acid, 5% sodium hydrogen carbonate and water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 1.6g.

e) Synthesis of 2', 3'-dideoxy-3'-fluoro-5'-O-{3-[1,3-bis-(L-valyloxy)-2-propyloxycarbonyl]-propanoyl} guanosine.

A solution of 2',3'-dideoxy-3'-fluoro-5'-O-{3-[1,3-bis-(N-CBZ-L-valyloxy)-2-propyloxycarbonyl)propanoyl} guanosine(1.6g, 1.75 mmole) in 80ml ethyl acetate, 20ml methanol and 20 ml acetic acid was hydrogenated with palladium black (0.3g) for two hours at room temperature and normal pressure. The catalyst was filtered and washed with methanol. The solution was evaporated under reduced pressure and the

product was isolated as the diacetate salt by silica gel column chromatography.Yield: 1.02g

^{1}H-NMR (DMSO d-6) 0.84 (m, 12H) 1.85(m, 2H) 2.58 (m, 4H) 2.60-3.10 (m, 2H) 3.11 (m, 2H) 3.61-4.39 (m, 7H) 5.19 (m, 1H) 5.35-5.56 (m, 1H) 6.16 (m, 1H) 6.62 (s, 2H) 7.89 (s,1H)

Example 4

<u>2', 3'-Dideoxy-3'-fluoro-5-O-[2-(-L-valyloxy)-propionyl]guanosine</u>

a) Synthesis of 2',3'-dideoxy-3'-fluoro-5-O-[2-(N-CBZ-L-valyloxy)-propionyl]guanosine.

A mixture of 2',3'-dideoxy-3'-fluoroguanosine (404mg, 1.5mmole), 2-(N-CBZ-L-valyloxy)-propionic acid (0.582g, 1.8 mmole), DMAP (22mg, 0.18 mmole) and HOBT (243mg, 1.8 mmole was coevaporated two times with DMF and reduced to about 30ml. DCC (412mg, 2.0 mmole) was added and the mixture was stirred overnight at room temperature. The mixture was filtered and the solution was evaporated under reduced pressure. 100ml ethyl acetate was added and the organic phase was washed twice with 5% acetic acid, with 5% sodium hydrogen carbonate and with water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography.Yield: 0.72g

b) Synthesis of 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propanoyl] guanosine

A solution of 2',3'-dideoxy-3'-fluoro-5-O-[2-(N-CBZ-L-valyloxy)-propanoyl] guanosine (0.6g, 1.04 mmole) in 20ml ethyl acetate, 10ml methanol and 10ml acetic acid was hydrogenated with palladium black (0.1g) for two hours at room temperature and normal pressure. The catalyst was filtered and washed with methanol. The solution was evaporated under reduced pressure to yield the title compound as the acetate salt. Yield: 0.5g

^{1}H-NMR (DMSO d-6) 0.88 (m, 6H) 1.40 (d, 3H) 1.92 (m, 4H) 2.52-3.04 (m, 2H) 3.18 (m, 1H) 4.18-4.42 (m, 3H) 5.06 (m, 1H) 5.32-5.58 (m, 2H) 6.18 (m, 1H) 6.52 (s, 2H) 7.90 (s, 1H)

Example 5

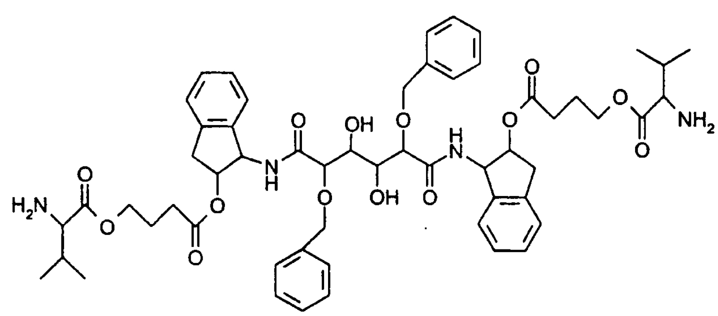
2', 3'-Dideoxy-3'-fluoro-5'-O-[2,3-bis-(L-valyloxy)propanoyl]guanosine

a) 2', 3'-Dideoxy-3'-fluoro-5'-O- [2,3-bis-(N-CBZ-L-valyloxy)propanoyl]guanosine

A mixture of 2', 3'-dideoxy-3'-fluoroguanosine (2.15g, 8 mmole), 2,3-bis-(N-CBZ-L-valyloxy)-propanoic acid (6.2g, 10.8 mmole), DMAP (244mg, 2 mmole) and HOBT (1.46g, 10.8 mmole) was coevaporated two times with DMF and reduced to about 120ml. DCC (2.48g, 12 mmole) was added and the mixture was stirred for two days at room temperature. The mixture was filtered and the solution was evaporated under reduced pressure. 150ml ethyl acetate was added and the organic phase was washed twice with 5% acetic acid, with 5% sodium hydrogen carbonate and with water. The organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography.
Yield: 2,25g = 35%
^{1}H-NMR (DMSO d-6) 0.88 (m,12H) 2,12 (m, 2H) 2.50-3.00 (m, 2H) 3.88-4.14 (m, 2H) 4.22-4.62 (m, 6H) 5.04 (s, 4H) 5.30-5.61 (m, 2H) 6.16 (m, 1H) 6.50 (s, 2H) 7.32 (m, 10H) 7.70 (m, 2H) 7.92 (s, 1H)

Example 6

N1,N6-*bis* {(1S,2R)-1-[2-(4-(L-valyloxy)-butanoyloxy)]-indanyl}-(2R,3R,4R,5R)-2,5-di(benzyloxy)-3,4-dihydroxyhexanediamide



a) N1,N6-*bis*{(1S,2R)-1-[2-(4-(N-Boc-L-valyloxy)-butanoyloxy)]-indanyl}-(2R,3R,4R,5R)-2,5-di(benzyloxy)-3,4-dihydroxyhexanediamide.

To N1,N6-bis [(1S,2R)-1-(2-hydroxy)-indany]-(2R,3R,4R,5R)-2,5-di-(benzyloxy)-3,4-dihydroxyhexanediamide from WO 98/45330 (326 mg, 0.5 mmole) and 4-(N-Boc-L-valyloxy)butyric acid (295 mg, 1 mmole) in dichloromethane (3 ml) were added 4-dimethylaminopyridine (12 mg, 0.1 mmole). The solution was cooled to -10° C and DCC (206 mg, 1 mmole) in dichloromethane (2 ml) was added dropwise over 2 hr. The reaction mixture was slowly warmed to room temperature, and kept for 18 hr. It was then filtered through Celite and poured into sodium bicarbonate aqueous solution. The organic phase was dried and the product was isolated with silica gel column chromatography. 103 mg.

b) N1,N6-bis{(1S,2R)-1-[2-(4-(L-valyloxy)-butanoyloxy)]-indanyl}-(2R,3R,4R,5R)-2,5-di(benzyloxy)-3,4-dihydroxyhexanediamide.

The intermediate of step a) (90 mg) was treated with trifluoroacetic acid (6 ml) at 0°C for 2 hr. The solution was dried and coevaporated with toluene and methanol successively, giving the titled product in quantitative yield.

^{1}H-NMR (DMSO-d6 + D_2O): 7.22 (m, 18H) 5.61 (m, 4H) 4.60-3.65 (m, 12H), 3.12 (dd, 4 H) 2.15 (m, 4H) 1.80 (m, 4H) 0.90 (m, 12 H).

Example 7

<u>N1-{(1S,2R)-2-[4-(L-valyloxy)butanoyloxy]-2,3-dihydro-1*H*-1-indenyl}-N6-[(1S)-2-methyl-1-(methylcarbamoyl)propyl]-(2R,3R,4R,5R)-2,5-di[4-(2-thiazolyl) benzyloxy] -3-hydroxy-4-[4-(L-valyloxy)butanoyloxy]hexanediamide *bis*-trifluoroacetate.</u>

a) N1-[(1S,2R)-2-Hydroxy-2,3-dihydro-1*H*-1-indenyl]-N6-[(1S)-2-methyl-1-(methylcarbamoyl)propyl]-(2R,3R,4R,5R)-2,5-di[4-(2-thiazolyl)benzyloxy]-3,4-dihydroxyhexanediamide.

A mixture of N1-[(1S,2R)-2-hydroxy-2,3-dihydro-1*H*-1-indenyl]-N6-[(1S)-2-methyl-1-(methylcarbamoyl)propyl]-(2R,3R,4R,5R)-2,5-di(4-bromobenzyloxy)-3,4-dihydroxyhexanediamide, prepared analagously to Example 11 of WO98/45330 using 4-bromobenzyl (130 mg, 0.164 mmol), tributyl-2-thiazolyltin (554 mg, 1.47

mmol), $PdCl_2(PPh_3)_2$ (120 mg, 0.5 M suspension in DMF), and dry DMF (3 ml) was twice degassed and flushed with argon and then stirred at 90°C/16h, evaporated to near dryness, washed with a little ether and purified by silica gel column chromatography (chloroform-methanol 20:1) to yield 95.5 mg (73 %) of off-white solid.

b) N1-{(1S,2R)-2-[4-(*N*-Boc-L-valyloxy)butanoyloxy]-2,3-dihydro-1*H*-1-indenyl}-N6-[(1S)-2-methyl-1-(methylcarbamoyl)propyl]-(2R,3R,4R,5R)-2,5-di[4-(2-thiazolyl)benzyloxy]-3-hydroxy-4-[4-(*N*-Boc-L-valyloxy)butanoyloxy] hexanediamide.

To obtain the di-acylated derivative, a solution of the intermediate of step a) (49.5 mg, 0.062 mmol), 4-(L-valyloxy)butyric acid (100 mg, 0.33 mmol), dicyclohexylcarbodiimide (50 mg, 0.24 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (10 mg, 0.082 mmol) in dichloromethane (1 ml) was kept at room temperature overnight. The precipitated dicyclohexylurea was filtered off and the solution evaporated to small volume and then purified by silica gel column chromatography (chloroform-hexane-methanol 20:10:1) to yield the title compound as a glass (71 mg, 84 %).

c) N1-{(1S,2R)-2-[4-(L-valyloxy)butanoyloxy]-2,3-dihydro-1*H*-1-indenyl}-N6-[(1S)-2-methyl-1-(methylcarbamoyl)propyl]-(2R,3R,4R,5R)-2,5-di[4-(2-thiazolyl)benzyloxy]-3-hydroxy-4-[4-(L-valyloxy)butanoyloxy]hexanediamide *bis*-trifluoroacetate.

The intermediate of step b) (71 mg, 0.0518 mmol) was dissolved in 1 ml of neat trifluoroacetic acid with cooling and kept at room temperature for 1h. The solution was evaporated to small volume, lyophilized with dioxane, then with water containing 10 % of dioxane, to give 66.6 mg (92 %) of the title compound as off-white, light powder.

^{13}C NMR ($CDCl_3$; 62.9 MHz) δ 17.5, 18.0, 23.6, 30.0, 31.1, 58.5, 65.0, 71.2, 71.6, 119.1, 123.2, 124.0, 126.8, 128.2, 128.5, 128.8, 133.4, 137.9, 139.3, 143.5, 161.7, 168.8, 169.1, 171.3.

Example 8

Application of a trifunctional linker to an hydroxyl bearing Drug

a) 6/18/20-O-mono-(6-(N-tritylvalyloxy)-5-(1-stearoyloxy methyl) hexanoyl) rifabutin

Dried rifabutin (343 mg, 0.42 mmol) and 6-(N-tritylvalyloxy)-5-(1-stearoyloxy methyl) hexanoic acid (323 mg, 0.42 mmol) were dissolved together in dry dichloromethane (3.5 ml). Then dimethylaminopyridine (6 mg, 0.05 mmol) and dicyclohexylcarbodiimide (93 mg, 0.45 mmol) were added and the reaction mixture was stirred for 24 h at 20° C. The mixture was filtered and extracted with 5% aqueous sodium bicarbonate and dichloromethane three times. The residue obtained by evaporation of the organic phase was chromatographed on silica gel and the product was eluted with 0%→2%EtOH / dichloromethane. (Yield 316 mg). R_f (5%MeOH / $CHCl_3$): 0.75.

b) 6/18/20-O-mono-(6-(valyloxy)-5-(1-stearoyloxy methyl) hexanoyl) rifabutin. The product from step a) (316 mg, 0.2 mmol) was dissolved in dioxane (2 ml) and then 80% acetic acid (20 ml) was added and the solution was stirred for 5 min at 20° C. The solution was evaporated and coevaporated with dioxane two times and toluene one time. The residue was chromatographed on silica gel and the product was eluted with 0%→5%EtOH / dichloromethane. (Yield 230 mg). R_f (5%MeOH / $CHCl_3$): 0.50.

^{1}H-NMR ($CHCl_3$): 8.35 (br, 1H); 7.77 (s, 1H); 6.42 (d,d, 1H); 6.12 (m, 2H); 5.91 (d,d, 1H); 5.12 (d, 1H); 5.07 (d,d, 1H); 4.94 (d, 1H); 4.18-3.96(m, 4H); 3.46 (d, 1H); 3.31 (d,d, 1H); 3.05 (s, 3H); 2.98 (m, 2H); 2.86 (d,d, 1H); 2.65 (m, 2H); 2.48 (q, 1H); 2.38-2.32 (m, 5H); 2.30 (s, 3H);); 2.13 (t, 2H); 2.05 (s, 3H); 2.01 (s, 3H); 2.00 (m, 2H); 1.85-1.73 (m, 11H); 1.78 (s, 3H); 1.68-1.50 (m, 5H); 1.25 (m, 28H); 1.15 (m, 2H); 1.05-0.85 (m, 21H); 0.47 (d, 3H); -0.18 (d, 3H).

Example 9

Application of a trifunctional linker to an alternative hydroxy Drug

a) Preparation of dibenzyl ester of 1,3-bis-(2-carboxychromon-5-yloxy)propan-2-ol. 1,3-bis(2-carboxychromon-5-yloxy)-propan-2-ol disodium salt (2.5g, 5.2 mmol), was suspended in DMF. To the suspension was added benzyl bromide (0.734 ml, 6.2 mmol) and the reaction was kept overnight under stirring. An additional portion of benzyl bromide (0.734 ml, 6.2 mmol) was added. After 24 hr, the reaction mixture was poured into sodium hydrogen carbonate aqueous solution and extracted dichloromethane. The organic phase was washed with water two times and evaporated to give the dibenzyl ester of 1,3-bis-(2-carboxychromon-5-yloxy)propan-2-ol (1.72 g).

b) Preparation of the dibenzyl ester of 2-[5-(N-trityl-L-valyloxymethyl)-6-stearoyloxyhexanoyloxy]-1,3-bis-(2-carboxychromon-5-yloxy)propane.
To a solution of the dibenzyl ester of 1,3-bis-(2-carboxychromon-5-yloxy)propan-2-ol (270 mg, 0.42 mmole), 5-(N-Trityl-L-valyloxymethyl)-6-stearoyloxyhexanoic acid (323 mg, 0.42 mmol) and dimethylaminopyridine (6 mg, 0.05 mmol) in dichloromethane was added DCC (92 mg, 0.45 mmol). After 3 days, the reaction mixture was filtered through Celite and the filtrate was washed with sodium hydrogen carbonate aqueous solution and dried. The product dibenzyl ester of 2-[5-(N-trityl-L-valyloxymethyl)-6-stearoyloxyhexanoyloxy]-1,3-bis-(2-carboxychromon-5-yloxy)propane was isolated from silica gel column chromatography. 250 mg.

c) Preparation of 2-[5-(L-valyloxymethyl)-6-stearoyloxyhexanoyloxy]-1,3-bis-(2-carboxychromon-5-yloxy)propane.
Dibenzyl ester of 2-[5-(N-trityl-L-valyloxymethyl)-6-stearoyloxyhexanoyloxy]-1,3-bis-(2-carboxychromon-5-yloxy)propane (238 mg, (0.17 mmol) was dissolved in ethyl acetate (1.5 ml). To the solution was added 80 % acetic acid (10 ml). After two hr, the solution was evaporated and purified by column chromatography to yield 197 mg of 2-[5-(L-valyloxymethyl)-6-stearoyloxyhexanoyloxy]-1,3-bis-(2-carboxychromon-5-yloxy)propane.

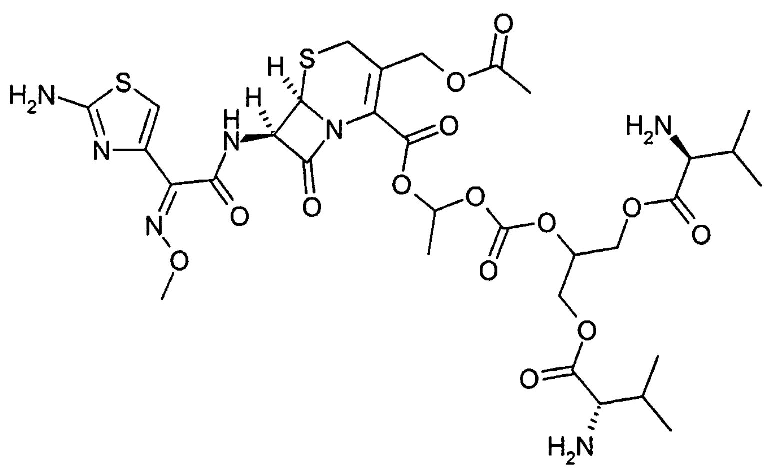
d) Preparation of 2-[5-(L-valyloxymethyl)-6-stearoyloxy-hexanoyloxy]-1,3-bis-(2-carboxychromon-5-yloxy)propane.

2-[5-(L-valyloxymethyl)-6-stearoyloxyhexanoyloxy]-1,3-bis-(2-carboxychromon-5-yloxy)propane (190 mg, 0.16 mmole) was dissolved in a mixed solvent of methanol (6 ml), ethyl acetate (2 ml) and acetic acid (0.5 ml) and hydrogenated on palladium black (30 mg) for 1 hr. After filtration, the solution was dried and coevaporated with toluene giving 160 mg titled product.

^{1}H-NMR (DMSO δ-6): 7.77 (t, 2 H), 7.27 (d, 2 H), 7.12 (d, 2 H), 6.68 (s, 2H), 5.60 (m, 1H), 4.60 (m, 4H), 4.05 (m, 5H), 2.50-2.10 (m, 6H), 1.90-1.50 (m, 6H), 1.26 (m, 28H), 0.93 (m, 9H).

Example 10

<u>1-[(1,3-bis(L-valyloxy)-2-propoxy)carbonyloxy]ethyl (7*R*)-3-acetoxymethyl-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate</u>



(a) a) 1-[(1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propoxy)carbonyloxy]ethyl (7*R*)-3-acetoxymethyl-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate

(b)

A solution of 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl 1-iodoethyl carbonate (0.156 mmol) and cefotaxime sodium (67.8 mg, 0.142 mmol) in 3.2 mL dry *N,N'*-dimethylformamide was stirred under argon for 22 h. The reaction mixture was concentrated and subjected to column chromatography (silica, 2/1 petroleum

ether – ethyl acetate, and then 20/1 CH_2Cl_2 – methanol) to yield an oil enriched in the desired product. The oil was dissolved in 10 mL ethyl acetate, washed with water, dried, and concentrated. A second chromatography (silica, 40/1 CH_2Cl_2 – methanol) gave the title compound (59.7 mg) as cream-colored solids.

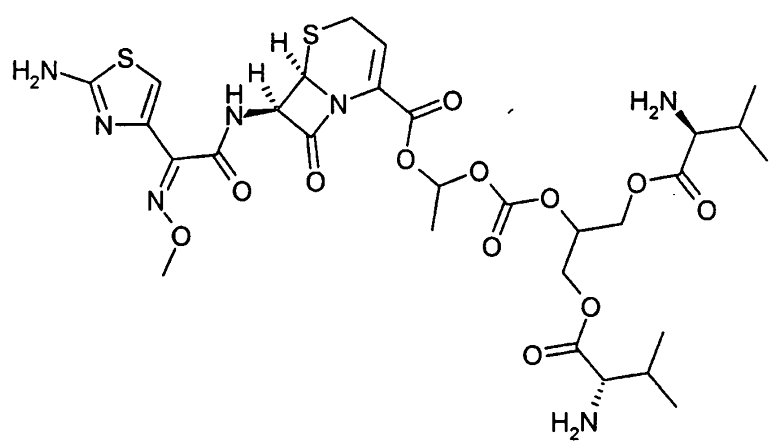
(c) b) 1-[(1,3-bis(L-valyloxy)-2-propoxy)carbonyloxy]ethyl (7*R*)-3-acetoxymethyl-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate.

(d) A solution of the Boc-protected cefotaxime ester (247 mg) prepared as in step (a) was dissolved in 1.5 mL CH_2Cl_2 and 1.5 mL CF_3COOH. After 7 min, the solvent was removed under vacuum to give fine, light yellow solids of the title compound as the trifluoroacetate salt.

^{1}H NMR (250 MHz, DMSO-d_6) δ 0.94-1.04 (m, 12H), 1.53 (d, 3H, J = 5.4 Hz), 2.07 and 2.08 (2s, 3H total), 2.19 (m, 2H), 3.57-3.77 (m, 2H), 3.92 (s, 3H), 4.03 (br s, 2H), 4.37-4.68 (m, 4H), 4.72-4.97 (ABq, 2H), 5.18-5.27 (br, 1H), 5.23 (d, 1H, J = 4.9 Hz), 5.88 (m, 1H), 6.80-6.95 (m, 2H), 8.50 (br s), 9.74 and 9.79 (2d, 1H total, J = 8.1 Hz).

Example 11

<u>1-[(1,3-bis(L-valyloxy)-2-propoxy)carbonyloxy]ethyl (*Z*)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylate</u>



a) 1-[(1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propoxy)carbonyloxy]ethyl (*Z*)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylate

A mixture of ceftizoxime sodium (550 mg, 1.36 mmol) and 1,3-bis(*N*-tert-butoxycarbonyl-L-valyloxy)-2-propyl 1-iodoethyl carbonate (1.5 mmol) in 27 mL dry DMF was stirred under nitrogen for 3 h. DMF was removed under vacuum and the residue was partitioned between ethyl acetate and water. The organic phase was washed successively with 5% $Na_2S_2O_3$ and brine, stirred with anhydrous Na_2SO_4 and activated carbon for 15 min, filtered through celite, and concentrated. Silica gel column chromatography (2/1 petroleum ether – ethyl acetate, 20/1 CH_2Cl_2 – methanol) yielded fractions enriched in the desired product. A second column chromatography (silica, 40/1 CH_2Cl_2 – methanol) gave the title compound (410 mg).

b) 1-[(1,3-bis(L-valyloxy)-2-propoxy)carbonyloxy]ethyl (*Z*)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylate.

The Boc-protected ceftizoxime ester (347 mg) from step (a) was dissolved in 2.5 mL CH_2Cl_2 and 2.5 mL CF_3COOH. After 15 min, the solvent was removed under vacuum to give fine light yellow solids of the title compound as the trifluoroacetate salt.

^{1}H NMR (250 MHz, DMSO-d_6) δ 0.95-1.04 (m, 12H), 1.54 (d, 3H, J = 5.4 Hz), 2.20 (m, 2H), 3.64-3.66 (m, 2H), 3.88 (s, 3H), 3.97 (br s, 2H), 4.37-4.66 (m, 4H), 5.15-5.20 (m, 2H), 5.87 (dd, 1H, J = 8.1, 5.0 Hz), 6.67 (m, 1H), 6.78 (s, 1H), 6.82 (q, 1H), 8.46 (br s), 9.54 and 9.55 (2d, 1H total, J = 8 Hz)

Example 12

<u>(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(L-isoleucyloxymethyloxy)-3-propionylphenyl] cyclopropyl}-N'-[2-(5-cyanopyridyl)]urea</u>

a) (1S, 2S)-N-{*cis*-2-[6-fluoro-2-(N-BOC-L-isoleucyloxymethyloxy)-3-propionylphenyl] cyclopropyl}-N'-[2-(5-cyanopyridyl)]urea.

To a solution of (1S, 2S)-N-{*cis*-2-[6-fluoro-2-hydroxy-3-propionylphenyl] cyclopropyl}-N'-[2-(5-cyanopyridyl)]urea prepared as shown in PCT/SE99/00053 (2.03 g, 5.5 mmol) in THF (50 mL) at 20 °C, was added NaH (60%, 220 mg, 5.5 mmol). After the mixture was stirred 1.5h at 20 °C, N-BOC-L-isoleucine iodomethyl ester (16.5 g, 16.5 mmol) was added. The solution was stirred for 6h at room temperature and then concentrated under reduced pressure. The crude product was

column chromatographed (aluminium oxide 90, 1% MeOH in CH_2Cl_2), to give 1.76 g of the title product.

b) (1S, 2S)-N-{*cis*-2-[6-fluoro-2-(L-isoleucyloxymethyloxy)-3-propionylphenyl] cyclopropyl}-N'-[2-(5-cyanopyridyl)]urea .

To TFA (30 mL) at 0 °C, was added (1S, 2S)-N-{*cis*-2-[6-fluoro-2-(N-BOC-L-isoleucyloxymethyloxy)-3-propionylphenyl] cyclopropyl}-N'-[2-(5-cyanopyridyl)]urea(1.81 g, 2.96 mmol). The reaction mixture was stirred at 0 °C for 30 min and then concentrated under reduced pressure at 0 °C. The crude product was column chromatographed (silica gel, 10% MeOH in CH_2Cl_2), to give 1.48 g of the title compound as the TFA-salt.

^{1}H-NMR ($CDCl_3$): 9.50 (br s, 1H), 9.42 (br s, 1H), 8.34 (s, 1H), 7.73 (dd, 1H), 7.27 (m, 1H), 7.10 (d, 1H), 6.81 (dd, 1H), 6.16 (d, 1H), 5.73 (d, 1H), 3.87 (d, 1H), 3.39 (m, 1H), 3.05-2.68 (m, 2H), 2.29 (dd, 1H), 2.10-1.88 (m, 2H), 1.57-1.21 (m, 3H), 1.09 (t, 3H), 1.02 (d, 3H), 0.91 (t, 3H).

Example 13

(1S, 2S)-N-{*cis*-2 [6 -fluoro-2-(L-valyloxymethyloxy)-3-propionylphenyl)] cyclopropyl}-N′-[2-(5-cyanopyridyl)]urea

a) (1S, 2S)-N-{*cis*-2-[6-fluoro-2-(N-CBz-L-valyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N′-[2-(5-cyanopyridyl)]urea

To a solution of (1S, 2S)-N-{*cis*-2-[6 -fluoro-2-hydroxy-3-propionylphenyl]cyclopropyl}-N′-[2-(5-cyanopyridyl)] urea (368 mg, 1 mmole) in THF (5 ml) was added sodium hydride in paraffin (60 %, 38 mg, 0.95 mmole). After 1.5 hour, N-CBz-L-valyloxymethyl iodide (1.09g, 2.8 mmole) prepared analogously to the N-BOC-L-isoleucyloxymethyl iodide described above was added to the solution and reaction was kept 18 hours. The mixture was filtered through Celite and poured into sodium hydrogen carbonate aqueous solution, and extracted with methylene chloride. The organic phase was dried and the product was isolated with silica gel column chromatography to yield 210 mg.

b) (1S, 2S)-N-{*cis*-2-[-fluoro-2-(L-valyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N′-[2-(5-cyanopyridyl)]urea

(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(N-CBz-L-valyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N′-[2-(5-cyanopyridyl)]urea (200 mg, 0.32 mmole) was dissolved in a mixed solvent of methanol (5 ml), ethylacetate (2 ml) and acetic acid (1 ml). To the solution was added palladium black (35 mg). It was kept under hydrogen at atmospheric pressure for two hours. After filtration, the solution was evaporated and the product was purified by silica gel column chromatography yielding 66 mg.

^{1}H-NMR ($CDCl_3$) 8.20 (d, 1H), 7.73 (dd, 1H), 7.44 (dd, 1H), 6.94 (m, 2H), 5.80 (dd, 2H), 3.37 (1H), 2.88 (m, 2H), 2.10 (m, 2H), 1.60 (m, 1H), 1.46 (m, 1H), 1.08 (t, 3H), 0.94 (m, 6H).

Example 14

(1S, 2S)-N-{*cis*-2 [6 -fluoro-2-(2,2-dimethyl-3-(L-valyloxy)-propionyloxy-methyloxy)-3-propionylphenyl]-cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea

a) (1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2,2-dimethyl-3-(N-Boc-L-valyloxy)propionyloxymethyloxy)-3-propionylphenyl]cyclopropyl}-N′-[2-(5-cyanopyridyl)]urea

To a solution of (1S, 2S)-N-[*cis*-2-(6 -fluoro-2-hydroxy-3-propionylphenyl) cyclopropyl]-N'-[2-(5-cyanopyridyl)] urea (368 mg, 1 mmole) in THF (5 ml) was added sodium hydride in paraffin (60 %, 38 mg, 0.95 mmole). After one hour, 2,2-dimethyl-3-(N-Boc-L-valyloxy)propionic acid iodomethyl ester (1.35g, 3 mmole) was added to the solution. After 5 hr at room temperature, it was then raised to 50 °C and reaction was kept 18 hours. The reaction mixture was poured into sodium hydrogen carbonate aqueous solution and extracted with methylene chloride. The organic phase was dried and the product was isolated with alumina column chromatography. 140 mg.

b) (1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2,2-dimethyl-3-(L-valyloxy)propionyl-oxymethyloxy)-3-propionylphenyl]-cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea

(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2,2-dimethyl-3-(N-Boc-L-valyloxy)-propionyloxymethyloxy)-3-propionylphenyl)] cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea (120 mg) was treated with trifluoroacetic acid at 0° C for 20 min. The solution was evaporated and coevaporated with toluene and methanol succesively, giving the titled product in quantitative yield.

^{1}H-NMR ($CDCl_3$): 8.33 (d, 1H) 7.89 (d, 1H) 7.48 (t, 1H) 7.16 (m, 1H) 6.96 (t, 1H) 5.70 (dd, 2H) 4.18 (dd, 2H) 4.01 (m, 1H) 3.38 (m, 1H) 2.88 (m, 2H) 2.16 (m, 1H) 1.58 (m, 2H) 1.25 (d, 6H) 1.04 (m, 9H).

Example 15

<u>(1S, 2S)-N-{*cis*-2-[6 -fluoro-2-(3,3-bis-(L-valyloxymethyl)propionyloxymethyloxy) -3-propionylphenyl]cyclopropyl}-N'-[2-(5-cyanopyridyl)]urea</u>

a) (1S, 2S)-N-{*cis*-2-[6-fluoro-2-(3,3-bis (N-CBz-L-valyloxymethyl) propionyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea

To a solution of (1S, 2S)-N-{*cis*-2-[6-fluoro-2-hydroxy-3-propionylphenyl] cyclopropyl}-N′-[2-(5-cyanopyridyl)] urea (331 mg, 1 mmole) in THF (5 ml) was added sodium hydride in paraffin (60 %, 32 mg, 0.81 mmole). After one hour, 3,3-bis-(N-CBz-L-valyloxymethyl) propionic acid iodomethyl ester (1.3g, 1.8 mmole) was added to the solution. After 5 hr at room temperature, it was then raised to 50 °C and reaction was kept 18 hours. The mixture was poured into sodium hydrogen carbonate aqueous solution, and extracted with methylene chloride. The organic phase was dried and the product was isolated with alumina column chromatography. 185 mg.

b) (1S, 2S)-N-{*cis*-2-[6 -fluoro-2-(3,3-bis (L-valyloxymethyl) propionyloxy-methyloxy)-3-propionylphenyl]cyclopropyl}-N'-[2-(5-cyanopyridyl)]urea

(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(3,3-bis (N-CBz-L-valyloxymethyl) propionyloxymethyloxy)-3-propionylphenyl]cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea (170 mg, 0.17 mmole) was dissolved in a mixed solvent of methanol (5 ml), ethyl acetate (2 ml) and acetic acid (1 ml). To the solution was added palladium

black (30 mg). It was kept under hydrogen at atmospheric pressure for four hours. After filtration, the solution was evaporated and the product was purified by silica gel column chromatography. 80 mg.

^{1}H-NMR (DMSO-d6): 8.38 (d, 1H) 8.02 (d, 1H) 7.42 (m, 2H) 7.12 (t, 1H) 5.70 (dd, 2H) 4.00 (s, 4H) 3.16 (m, 1H) 3.08 (d, 2H) 2.80 (m, 1H) 2.40 (m, 2H), 2.11 (m, 1H) 1.52 (m, 1H) 0.95 (t, 3H) 0.98 (dd, 12 H).

Example16

(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2-(L-valyloxy)-ethoxycarbonyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N′-[2-(5-cyanopyridyl)] urea

a) (1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2-(N-CBz-L-valyloxy)-ethoxycarbonyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea

To a solution of (1S, 2S)-N-{*cis*-2 [6-fluoro-2-hydroxy-3-propionylphenyl] cyclopropyl}-N′-[2-(5-cyanopyridyl)]urea (368 mg, 1 mmole) in THF (5 ml) was added sodium hydride in paraffin (60 %, 38 mg, 0.95 mmole). After 1.5 hr, 2- (N-CBz-L-valyloxy)ethoxycarbonyloxymethyl iodide (864 mg, 1.7 mmole) was added to the solution. The reaction was kept for 48 hours. The mixture was poured into sodium hydrogen carbonate aqueous solution, and extracted with methylene chloride. The organic phase was dried and the product was isolated with silica gel column chromatography. 210 mg.

^{1}H-NMR ($CDCl_3$): 8.21 (d, 1H) 7.72 (d, 1H) 7.28 (m, 6H) 6.90 (m, 2H) 5.75 (dd, 2H) 5.09 (s, 2H) 4.35 (m, 4H) 2.85 (m, 2H) 2.50 (m, 2H) 2.16 (m, 1H), 1.65 (m, 1H) 1.11 (t, 3H) 0.93 (dd, 6 H).

b) 1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2-(L-valyloxy)-ethoxycarbonyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N′-[2-(5-cyanopyridyl)] urea.

(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2-(N-CBz-L-valyloxy)-ethoxycarbonyloxymethyl oxy)-3-propionylphenyl)]cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea is deprotected by conventional techniques such as palladium black in a mixed solvent of methanol, ethyl acetate and acetic acid under hydrogen at atmospheric pressure followed by

conventional work up such as filtration, evaporation and silica gel column chromatorgraphy.

Example 17

(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(1,3-bis-L-valyloxy-2-(propoxycarbonyloxymethyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea

a) (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(1,3-bis-(N-BOC-L-valyloxy-2-(propoxycarbonyloxymethyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea.

NaH (121 mg, 60% w/w in mineral oil, 3.0 mmol) was added to a mixture of (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea (1.05 g, 2.85 mmol) in 15 mL dry THF under N_2. After 1 h, the solution was concentrated to dryness and redissolved in 10 mL DMF. 2-*O*-iodomethoxycarbonyl-1,3-di-*O*-(*N*-tert-butoxycarbonyl-L-valyl)glycerol (2.96 g, 4.39 mmol) in 15 mL DMF was added and the reaction mixture was stirred for 20 h. Removal of solvent under vacuum followed by flash column chromatography (silica gel, 2/1 ethyl acetate - petroleum ether) gave 1.46 g (56%) of the title product as a white solid.

b) (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(1,3-bis-L-valyloxy-2-(propoxycarbonyloxymethyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea.

Ice-cold trifluoroacetic acid (30 mL) was added to the intermediate of step a (1.69 g, 1.85 mmol) in an ice bath, under N_2. After 7 min, the reaction mixture was concentrated under vacuum, coevaporating several times with, initially, toluene and, finally, CH_2Cl_2. The oily residue was chromatographed immediately on a silica gel column with 10-20 % methanol in CH_2Cl_2 to give 1.37 g of the product as a trifluoroacetate salt.

^{1}H NMR (250 MHz, CD_3OD) δ 1.07-1.12 (m, 15H), 1.26 (m, 1H), 1.63 (m, 1H), 2.19 (m, 1H), 2.35 (m, 2H), 2.89 (m, 2H), 4.08 (m, 2H), 4.44-4.71 (m, 4H), 5.26 (m, 1H), 5.79 and 5.91 (AB q, 2H), 7.10-7.18 (m, 2H), 7.59 (dd, 1H), 7.93 (dd, 1H), 8.30 (d, 1H).^{19}F NMR (235 MHz, CD_3OD) δ -103.5, -73.5.

Example 18

(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(L-valyloxy)methoxycarbonyloxy-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea

a) (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-chloromethoxycarbonyloxy-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea

Chloromethyl chloroformate (2.3 mL, 25 mmol) was added by syringe to a mixture of (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea (4.695 g, 12.7 mmol) and pyridine (6.1 mL, 76 mmol) in 65 mL dry CH_2Cl_2 with cooling in an ice bath, under N_2. After 10 min, the ice bath was removed and the mixture was stirred at room temperature for 1h 40 min. The mixture was diluted with 100 mL CH_2Cl_2 and washed with 50 mL H_2O. The aqueous phase was reextracted with 25 mL CH_2Cl_2. The combined organic phases were washed with 50 mL saturated $NaHCO_3$, followed by 2 x 50 mL brine. Drying over Na_2SO_4 and concentration under vacuum gave a crude material that was subjected to flash column chromatography (silica gel, 1/1 ethyl acetate - petroleum ether) to give 4.05 g (69%) title product.

^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (t, 3H), 1.30 (m, 1H), 1.59 (m, 1H), 2.02 (m, 1H), 2.87 (q, 2H), 3.29 (m, 1H), 5.87 (s, 2H), 6.97 (d, 1H), 7.09 (m, 1H), 7.72 (dd, 1H), 7.76 (dd, 1H), 8.10 (dd, 1H), 9.26 (br s, 1H), 10.09 (brs, 1H).

b) (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-iodomethoxycarbonyloxy-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea

(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-chloromethoxycarbonyloxy-3-propionylphenyl) cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea (3.97 g, 8.6 mmol) and NaI (5.17 g, 34.5 mmol) in 85 mL dry acetonitrile were refluxed at 70 °C for 4 h under N_2. The solvent was removed *in vacuo*, the residue was partitioned between 100 mL CH_2Cl_2 and 25 mL H_2O, the aqueous phase was reextracted with 10 mL CH_2Cl_2, and the organic phases were combined, washed successively with 2 x 25 mL 5% $Na_2S_2O_3$ and 2 x 25 mL brine, and dried over Na_2SO_4. Flash column chromatography (silica gel, 2/1 ethyl acetate - petroleum ether) of the crude product obtained after concentration *in vacuo* gave 4.15 g material containing 92% of the title compound and traces of the starting material.

^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (t, 3H), 1.34 (m, 1H), 1.62 (m, 1H), 2.03 (m, 1H), 2.86 (q, 2H), 3.32 (m, 1H), 6.08 (s, 2H), 6.97 (d, 1H), 7.08 (m, 1H), 7.70-7.76 (m, 2H), 8.13 (d, 1H), 8.90 (br s, 1H), 9.30 (br s, 1H).

c) (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(N-BOC-L-valyloxy)methoxycarbonyloxy-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea

Tetrabutylammonium hydroxide (40 wt % solution in water, 6.4 mL, 9.8 mmol) was added to Boc-L-valine (2.54 g, 11.7 mmol) in 30 mL dioxane. The solution was concentrated *in vacuo*, coevaporating several times with dioxane, toluene, and CH_2Cl_2, and dried under vacuum overnight. The resulting Q salt was dissolved in 30 mL dry CH_2Cl_2 and (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(iodomethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea (7.1 mmol) in 65 mL dry CH_2Cl_2 was added. After stirring under N_2 for 18 h, the reaction mixture was washed with 3 x 50 mL H_2O, 1 x 50 mL 5% $Na_2S_2O_3$, and 2 x 50 mL H_2O. The organic phase was dried over Na_2SO_4, concentrated, and submitted to flash column chromatography (silica gel, 3/1 ethyl acetate - petroleum ether) to give 2.21 g (49%) product.

^{1}H NMR (250 MHz, CD_3OD) δ 0.98 (d, 3H), 1.02 (d, 3H), 1.17 (t, 3H), 1.24 (m, 1H), 1.47 (s, 9H), 1.59 (m, 1H), 2.06 (m, 1H), 2.24 (m, 1H), 2.96 (q, 2H), 3.24 (m. 1H), 4.15 (d, 1H), 5.94 and 6.02 (AB q, 2H), 7.12 (d, 1H), 7.26 (m, 1H), 7.91 (dd, 1H), 7.94 (dd, 1H), 8.23 (dd, 1H).

d) (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(L-valyloxy)methoxycarbonyloxy-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea

Cold trifluoroacetic acid (40 mL) was added to (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(N-BOC-L-valyloxymethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea (1.94 g, 3.02 mmol) with cooling in an ice bath, under N_2. After 5 min, the solution was concentrated *in vacuo*, coevaporating several times with toluene, and then CH_2Cl_2, and dried under vacuum for several hours to give the compound as a trifluoroacetate salt in quantitative yield.

^{1}H NMR (250 MHz, CD_3OD) δ 1.12-1.18 (m, 9H), 1.25 (m, 1H), 1.59 (m, 1H), 2.07 (m, 1H), 2.47 (m, 1H), 2.97 (q, 2H), 3.26 (m, 1H), 4.16 (d, 1H), 6.01 and 6.37 (AB q, 2H), 7.11 (d, 1H), 7.29 (m,1H), 7.92 (dd, 1H), 7.99 (dd, 1H), 8.22 (d, 1H).
^{19}F NMR (235 MHz, CD_3OD) δ -102.7, -74.0.

Example 20

(1S, 2S)-N-{*cis*-2 [6 -fluoro-2-(3-carboxylpropionyloxymethyloxy)-3-propionylphenyl]cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea

a) (1S, 2S)-N-{*cis*-2-[6 -fluoro-2-(3 -benzyloxycarbonylpropionyl-oxymethyloxy)-3-propionylphenyl]cyclopropyl}-N′-[2-(5-cyanopyridyl)]urea.
3-Benzyloxycarbonylpropionic acid iodomethyl ester (522 mg, 1.5 mmole) was added to a solution of (1S, 2S)-N-{*cis*-2-[6 -fluoro-2-hydroxy-3-propionylphenyl] cyclopropyl}-N′-[2-(5-cyanopyridyl)] urea (185 mg, 0.5 mmole) in THF (5 ml) which had been treated with sodium hydride in paraffin (60 %, 20 mg, 0.5 mmole) for 30 min. After 18 hr at room temperature, the reaction mixture was poured into sodium hydrogen carbonate aqueous solution, and extracted with methylene chloride. The organic phase was dried and the product was isolated with alumina column chromatography. 115 mg.

b) (1S, 2S)-N-{*cis*-2-[6-fluoro-2-(3-carboxylpropionyloxymethyloxy)-3-propionylphenyl]cyclopropyl}-N′-[2-(5-cyanopyridyl)] urea
(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(3-carboxylpropionyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N'-[2-(5cyanopyridyl)] urea (100 mg, 0.17 mmole) was dissolved in a mixed solvent of ethylacetate (3 ml) and acetic acid (1 ml). To the solution was added palladium black (30 mg). It was kept under hydrogen at atmospheric pressure for three hours. After filtration, the solution was evaporated and the product was purified by silica gel column chromatography. 81 mg.
^{1}H-NMR ($CDCl_3$): 8.21 (s, 1H) 7.75 (d, 1H) 7.49 (dd, 1H) 7.08 (d, 5H) 6.97 (t, 1H) 5.73 (dd, 2H) 5.17 (s, 2H) 3,26 (m, 1H) 2.87 (m, 2H) 2.60 (m, 4H) 2.09 (m, 1H) 1.58 (m, 1H) 1.11 (t, 3H)

Example 21

(1S, 2S)-N-[*cis*-2-(6-fluoro-2-O-(4-L-valyloxybenzoyl)-3propionylphenyl)-cyclopropyl]-N'-(5-cyanopyrid-2-yl) urea

a) 4-benzyloxybenzoic acid.

To a solution of 4-hydroxybenzoic acid (6.9g, 50 mmole) in 150 ml DMF was added potassium tert.-butoxide (12.34g, 110 mmole) and the mixture was stirred at room temperature for one hour. Benzyl bromide (20.5g, 120 mmole) was added and the mixture was stirred for two days at room temperature. The mixture was evaporated under reduced pressure and 100ml 1,4-dioxane and a solution of sodium hydroxide (6.0g, 150 mmole)in 50 ml water was added. The mixture was refluxed for two hours, cooled and evaporated under reduced pressure. Water was added and the mixture was acidified with acetic acid. The product was filtered, washed with cold water and dried. Yield: 10.2g = 89%.

b) 4-benzyloxybenzoyl chloride.

To a mixture of 4-benzyloxybenzoic acid (2.28g, 10 mmole) in 20 ml dried dichloromethane were added five drops of DMF and 2.5 ml thionyl chloride. The mixture was refluxed for three hours and evaporated under reduced pressure. Yield: 2.45g = 100%

c) (1S, 2H)-N-[*cis*-2-(6-fluoro-2-O-(4-benzyloxybenzoyl)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyrid-2-yl) urea .

To a solution of (1S, 2S)-N-[*cis*-2-(6-fluoro-2-hydroxy-3-propionylphenyl) cyclopropyl]-N'-(5-cyanopyrid-2-yl) urea (184mg, 0.5 mmole) in 3 ml DMF was added potassium tert. butoxide (78.5mg, 0.7 mmole) and the mixture was stirred for one hour at room temperature. A solution of 4-benzyloxybenzoylchloride (185mg, 0.75 mmole) in 1ml DMF was added and the mixture was stirred overnight at room temperature. 40 ml ethyl acetate were added and the organic phase was washed four times with water. The solution was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 180mg = 62%.

d) (1S, 2S)-N-[*cis*-2-(6-fluoro-2-O (4-hydroxybenzoyl)-3-propionylphenyl) cyclopropyl]-N'-(5-cyanopyrid-2-yl)] urea-O-4-hydroxybenzoate

A solution of the intermediate of step c) (170 mg, 0.29 mmole) in 15 ml ethyl acetate and 15 ml methanol was hydrogenated with 10% palladium on charcoal (30mg) three times at room temperature and normal pressure. The catalyst was filtered and washed with ethyl acetate and methanol and the solution was evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 100 mg = 70%.

^{1}H-NMR (DMSO δ-6) 0.93 (m, 4H) 1.32 (m, 1H) 1.88 (m,1H) 2.85 (m, 2H) 3.05 (m, 1H) 6.92 (m, 2H) 7.38 (m, 2H) 8.00 (m, 4H) 8.38 (m, 1H)

e) (1S, 2S)-N-[*cis*-2-(6-fluoro-2-O (4-L-valyloxybenzoyl)-3-propionylphenyl)-cyclopropyl]-N'-(5-cyanopyrid-2-yl) urea.

An R_2 group, such as N-protected L-valyl is acylated to the exposed ring hydroxy group using conventional acylation conditions as described herein and deprotected to yield a compound of the invention.

Example 22

<u>(1S, 2S)-N-[*cis*-2-(6-fluoro-2-O ((4-isoleucyloxybenzoyloxymethyl)-3-propionylphenyl)-cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea-O-methylene-4-hydroxybenzoate-O-L-isoleucyl ester</u>

a) Methyl-4-(4-methoxybenzyloxy) benzoate.

To a solution of methyl 4-hydoxybenzoate (6.85g, 45 mmole) in 80 ml DMF was added potassium tert. butoxide (5.6 g, 51 mmole) and the mixture was stirred at room temperature for one hour. 4-Methoxybenzyl chloride (8.3 g, 52 mmole) was added and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and 200 ml ethyl acetate was added. The organic phase was washed four times with water, dried with sodium sulfate and evaporated under reduced pressure. Yield: 12.3g = 100%

b) 4- (4-methoxybenzyloxy) benzoic acid

To a solution of methyl 4-(4-methoxybenzyloxy) benzoate (12.2 g, 44.8 mmole) in 50 ml 1,4-dioxane was added a solution of lithium hydroxide (2.15 g, 89,6 mmole) and the mixture was stirred overnight at 60°C. The mixture was evaporated under reduced pressure and 5% acetic acid was added. The product was filtered, washed with water and dried. Yield: 10.1g = 87%

c) Chloromethyl 4-(4-methoxybenzyloxy)benzoate

To a solution of 4-(4-methoxybenzyloxy) benzoic acid (5.16 g, 20 mmole) in 100 ml 1,4-dioxane was added a 40% solution of tetrabutylammonium hydroxide (14.27 g, 22 mmole) and the mixture was stirred 2 hours at room temperature. The mixture was evaporated under reduced pressure and co-evaporated two times with 1,4-dioxane and two times with toluene. The dried product was dissolved in 60 ml dichloromethane and iodochloromethane (35.3 g 200 mmole) was added. The solution was stirred for two days at room temperature and evaporated under reduced pressure. About 100 ml ethyl actate was added and the organic phase washed twice with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography.Yield: 4.48 g = 73%

d) Iodomethyl 4-(4-methoxybenzyloxy) benzoate

To a solution of chloromethyl 4-(4-methoxybenzyloxy) benzoate (0.77g, 2.5 mmole) in 15 ml dry acetone was added sodium iodide (1.87g, 12.5 mmole) and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and extracted with ethyl actate/water. The organic phase was washed with a 5% sodium thiosulfate solution, dried with sodium sulfate and evaporated under reduced pressure. Yield 0.86g = 86%

e) (1S, 2S)-N-[*cis*-2-(6-fluoro-2-O-(4(4-methoxybenzyloxy)-benzoyloxymethyl)-3-propionylphenyl (cyclopropyl] -N'-[2-(5-cyanopyridyl)urea

To a solution of (1S, 2S)-N-[*cis*-2-(6-fluoro-2-hydroxy-3-propionylphenyl) cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea (368mg, 1 mmole) in 5 ml DMF was added a suspension of 60% sodium hydride in mineral oil (44mg, 1.1 mmole) and the mixture was stirred for one hour at room temperature. A solution of iodomethyl-4-(4-

methoxybenzyloxy) benzoate (0.84 g, 2.1 mmole) in 2 ml THF was added and the mixture was stirred overnight at room temperature. 50 ml ethyl acetate were added and the organic phase was washed four times with water, dried with sodium sulfate and evaporated under reduced pressure. The product was isolated by silica gel column chromatography. Yield: 525 mg = 82%

f) (1S, 2S)-N-[*cis*-2-(6-fluoro-2-O (4-hydroxybenzoyloxymethyl)-3-propionylphenyl)cyclopropyl]-N'- [2-(5-cyanopyridyl)]urea-O-methylene-4-hydroxybenzoate

To a solution of the intermediate of step e) (100 mg, 0.156 mmole) in 4 ml dichloromethane was added TFA (0.5 ml) and the solution was stirred for one hour at room temperature. The solution was evaporated under reduced pressure and the product was isolated by silica gel column chromatography. Yield: 45mg = 55%. ^{1}H-NMR (DMSO δ-6) 0.84 (m, 3H) 1.10 (m, 1H) 1.48 (m, 1H) 2.12 (m, 1H) 2.80 (m, 2H) 3.19 (m, 1H) 5.85-6.02 (m, 2H) 6.84 (m, 2H) 7.18 (m, 1H) 7.46 (m, 2H) 7.74 (m, 2H) 8.04 (m, 2H) 8.38 (m, 1H)

g) (1S, 2S)-N-[*cis*-2-(6-fluoro-2-O (4-isoleucyloxybenzoyloxymethyl)-3-propionylphenyl)-cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea-O-methylene-4-hydroxybenzoate-O-L-isoleucyl ester

An R_2 group, such as N-protected L-isoleucine is acylated to the exposed hydroxy group using conventional acylation condtions as described herein and deprotected to yield a compound of the invention.

Biological Example 1

Pharmacokinetics

Confirmation that orally administered prodrugs as envisaged by the invention release the respective mother compound in vivo is obtained in a rat model which is recognized as a useful model for assessing pharmacokinetic parameters of nucleoside analogues. The oral compositions are administered in a pharmaceutical vehicle comprising propylene glycol, or in the case of the more soluble compounds such as that of Example 26 or Example 34, in water, to duplicate fasted animals in a dosage

corresponding to 0.1 mmol/kg. For comparison, a set of rats is iv dosed with 0.01 mmol/kg of the metabolite 2',3'-dideoxy-3'-fluoroguanosine. Serum levels of the metabolite are then monitored in serum collected at intervals from individual animals from 0.5 to up to 12 hours following administration (5 min to 6 hours for FLG).

The metabolite is analysed with HPLC with UV detection at 254 nm, in a manner analogous to Ståhle et al 1995, J Pharm. Biomed. Anal. 13, 369-376. An HPLC system can be based on a 0.05 M ammonium-dihydrogen-phosphate buffer, with 1.2 % 2-propanol solvent, buffered to pH 4.5 or 30 mM sodium dihydrogen phosphate buffer with 2% acetonitrile solvent buffered to pH 7.0. The column may be a 100 x 2.1 mm BAS C18 5 μm particle size with a 7 μm C18 guard column or Zorbax SB-CN C18 150x4.6mm, 5μm column. Protein binding of the compounds of the invention is neglible as is that of the metabolite and ultrafiltration through Amicon or Microcon 30 filters is useful for serum samples. Advantageously the main peak is subject to further column chromatography to better aid in resolution of FLG over low weight serum components. The iv levels are multiplied by a factor of ten in order to obtain AUC values for comparison with the oral values. Absolute oral bioavailability is determined as the ratio between ${}^{0-\infty}AUC_{iv}$ and ${}^{0-\infty}AUC_{oral}$.

Table 1

	6h absolute bioavail. %	12h absolute bioavail. %
FLG		9%**
5'-O- [3,3-bis (L-valyloxymethyl)-propionyl] FLG	67%	
5'-O-[2-(-L-valyloxy)-propionyl]FLG	68%	
5'-O- [3,3-bis (L-valyloxymethyl)-propionyl] FLG		67.5%
5'-O-3-[1,3-bis-(L-valyloxy)-2-propyloxycarbonyl propanoyl]FLG	51%	

* estimated. **literature value

The compounds of the invention thus provide significantly enhanced oral bioavailability relative to the active metabolite 2',3'-dideoxy-3'-fluoroguanosine. Notably, the compounds are released into the blood in a relatively sustained manner, rather than in an immediate peak. This means that effective amounts of the active metabolite are available in the blood for many hours assisting once daily dosage. Additionally, a sustained release avoids the problems of acute toxicity seen in compounds with a more rapid release rate.

Although the rat is well recognized as a good model for predicting human bioavailability of nuceoside analogues, species independent bioavailability of a 5'-O-3-[1,3-bis-(L-valyloxy)-2-propyloxycarbonyl propanoyl]FLG was confirmed in ≅11.5 kg male and female beagle dogs administered orally with 0.05 mmol/kg (38 mg/kg) compound in water or iv 0.005 mmol/kg (1.35 mg/kg) metabolite in water. Plasma collection and analysis as above.

Male dog	12 hour absolute bioavailability	51%
Female dog	12 hour absolute bioavailability	74%

Biological Example 2

Bioavailability

The release of the phenolic mother compound from a prodrug of the invention were monitored in rats. The compounds of Examples P1-4, 6&7 were made up in a propylene glycol vehicle and orally administered to paired fasted male Sprague Dawley rats at a dose corresponding to 0.027 mmol/kg. At 30, 60, 120, 240 & 360 minutes, 0.2 ml blood were collected, centrifuged and frozen for later analysis. The released phenolic drug, (1S, 2S)-N-[*cis*-2-(6 -fluoro-2-hydroxy-3-propionylphenyl) cyclopropyl]-N'-[2-(5-cyanopyridyl)] urea was assayed by HPLC. Aliquots comprising 40-100 μl of each plasma sample are mixed with an equal volume of

acetonitrile (10 seconds, Vibrofex). The sample is centrifuged (2 min, 14000 RPM) and 30 μl of the supernatant is injected into an HPLC system, as follows.

Pre column:	RP-18, 7 μm, 15 x 3.2 mm
Column:	YMC basic, 3μm, 150 x 3 mm
Mobile phase:	60 % acetonitrile in 3 mM ammonium acetate, pH 6.4
Flow rate:	0.4 ml/min
Detection:	UV, 250 nm

TABLE P-1

Example	$\text{Bioavailability}_{0\text{-}6\text{ hours}}$
P-1	34 %
P-2	18 %
P-3	27 %
P-4	18 %
P-6	50 %
P-7	70 %

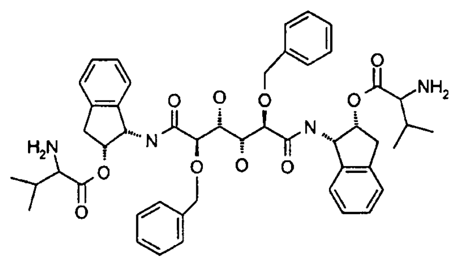
The above bioavailabilities correspond to sustained plasma levels of the active metabolite well above the ED_{50} for HIV-1.

Biological Example 3

Bioavailability of the ring indanolic ring hydroxy compound of Example B-1 was assessed in rats by the procedure of Biological Example 2 also using a propylene glycol vehicle, 58mg/kg (0.047 mmol/kg), but wherein the mother compound N1, N6-di [(1S,2R)-2-hydroxy-2,3-dihydro-1-*H*-1-indenyl]-(2R, 3R, 5R)-2,5-di(benzyloxy)-3,4-dihydroxyhexanediamide was assayed by LC-MS using SiM (single ion monitoring) with M/Z ion detector 653. Plasma results are presented as μM in the table below:

Time	Rat 1	Rat 2	Rat 3
0	<0.02	<0.02	<0.02
0.5	0.17	0.46	0.23
1	0.73	1.4	1.22
2	0.86	1.7	1.09
4	0.52	0.67	0.43
6	0.23	0.24	0.08

The average bioavailability is thus 57%. This should be contrasted with the bioavailability of the mother compound (below level of detection). Interestingly, the bioavailability of the analogue bearing R_2 groups (depicted immediately below) but lacking the linker component of the invention was also below the level of detection in the same assay:



CLAIMS

1. A pharmaceutical compound or an intermediate therefor, having the formula:

$$D^*\text{-Linker}^*\ (R_2')_k\text{-}R_2$$

where R_2 and R_2' (if present) is the amide or ester residue of an aliphatic amino acid,

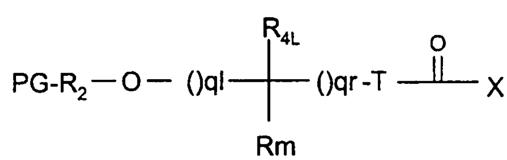
k is 0 or 1,

D* is a Drug residue bearing an accessible function selected from amine, hydroxy and carboxy, or a group amenable to attachment to said accesible function,

Linker* is an at least bifunctional linker comprising a first function bound to said accessible function spaced from a second function forming an amide or acyl bond with the aliphatic amino acid;

wherein the compound is free from long chain fatty acid esters; and with the provisos that Linker* does not consist solely of alkoxy when the Drug comprises a lactamcarboxy or enolic hydroxy function and that the Drug is not a monohydric nucleoside.

2. A compound according to claim 1, with the formula:



wherein

PG-R_2 is the acyl residue of an aliphatic amino acid, optionally N-protected,

R_{4L} is H, C_{1-3} alkyl or phenyl,

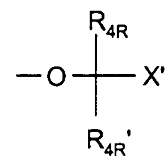
Rm is H, C_{1-3} alkyl, phenyl or -$()_m$-O-R_2

ql is 0-3, qr is 0-3, m is 0-2

T is a bond, -NR_4- or -O-

R_4 is H or C_{1-3}alkyl;

X is OH, an activating group, an ester linkage to a Drug bearing an accessible hydroxy function, an amide linkage to a Drug bearing an accessible amine function or a structure of the formula:



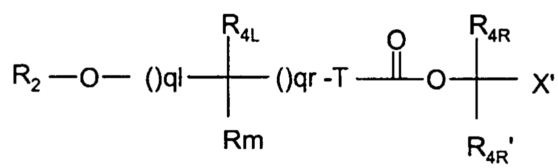
where

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl; and

X' is halo or an ether linkage to a drug bearing an accessible hydroxy function or an ester linkage to a Drug bearing an accessible carboxy function;

and pharmaceutically acceptable salts thereof.

3. A compound according to claim 2, with the structure:



4. A compound according to claim 3, wherein R_{4R} and R_{4R}' are hydrogen.

5. A compound according to claim 3 wherein R_{4R} and R_{4R}' are methyl.

6. A compound according to claim 3 wherein R_{4R} is H and R_{4R}' is methyl.

7. A compound according to claim 3, wherein R_{4L} and Rm are respectively: methyl, methyl;
methyl, hydrogen; or
ethyl, ethyl.

8. A compound according to claim 3 wherein R_{4L} and Rm are H

9. A compound according to claim 3 wherein R_{4L} is H and Rm is -()m-O-R2.

10 A compound according to claim 3, wherein ql and qr are respectively

1,0;

2,0;

3,0;

4,0;

11 A compound according to claim 3, wherein ql and qr are respectively

1,1;

2,1;

3,1;

4,1; or

2,2.

12 A compound according to claim 3, wherein T is a bond.

13 A compound according to claim 3, wherein T is -NH-.

14 A compound according to claim 3, wherein T is -O-.

15 A compound according to claim 3, wherein PG-R_2 is derived from L-valyl or L-isoleucyl.

16 A compound according to claim 3 wherein X' is halo and PG-R_2 is N-Fmoc-L-valyl, N-Boc-L-valyl, N-CBz-L-valyl, N-Fmoc-L-isoleucyl, N-Boc-L-isoleucyl or N-CBz-L-isoleucyl.

17 A compound according to claim 15, selected from:

2,2-dimethyl-3-(N-PG-L-valyloxy)propionic acid iodomethyl ester

2-(N-PG-L-valyloxy)ethoxycarbonyloxymethyl iodide

3,3- bis (N-PG-L-valyloxymethyl)-propionic acid iodomethyl ester,

Iodomethyl 1,3-bis(N-PG-L-valyloxy)-2-propyl carbonate,

1,3-bis(*N*-PG-L-valyloxy)-2-propyl 1-iodoethyl carbonate

Iodomethyl 2-methyl-2-(N-PG-L-valyloxymethyl) propionate,

Iodomethyl 2-(N-PG-L-valyloxy)-DL-propionate.

Iodomethyl 2-(N-PG-L-valyloxy)isobutyrate.

Iodomethyl 2-(N-PG-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

Iodomethyl 2-O-(N-PG-L-valyloxy)-2-phenyl-DL-acetate

Iodomethyl 5-(N-PG-L-valyloxy)-2,2-dimethylvalerate

2-(N-PG-L-valyloxy)-ethyl iodomethyl carbonate

4-(N-PG-L-valyloxy) butyric acid iodomethyl ester

Iodomethyl-3-(N-PG-L-valyloxy)-propionate

3-(*N*-PG-L-valyloxy)-2,2-dimethylpropyl iodomethyl carbonate

Iodomethyl 2-(N-PG-L-valyloxymethyl)-2-ethyl butyrate

2-(N-(iodomethoxycarbonyl)-amino)-2-methyl-1-(N-PG-L-valyloxy)-propane

2,2-dimethyl-3-(N-PG-L-isoleucyloxy)propionic acid iodomethyl ester

2-(N-PG-L-isoleucyloxy)ethoxycarbonyloxymethyl iodide

3,3- bis (N-PG-L-isoleucyloxymethyl)-propionic acid iodomethyl ester

Iodomethyl 1,3-bis(N-PG-L-isoleucyloxy)-2-propyl carbonate

1,3-bis(*N*-PG-L-isoleucyloxy)-2-propyl 1-iodoethyl carbonate

Iodomethyl 2-methyl-2-(N-PG-L-isoleucyloxymethyl) propionate,

Iodomethyl 2-(N-PG-L-isoleucyloxy)-DL-propionate.

Iodomethyl 2-(N-PG-L-isoleucyloxy)isobutyrate.

Iodomethyl 2-(N-PG-L-isoleucyloxy)-3-methyl-(S)-(+)-butyrate.

Iodomethyl 2-(N-PG-L-isoleucyloxy)-2-phenyl-DL-acetate

Iodomethyl 5-(N-PG-L-isoleucyloxy)-2,2-dimethylvalerate

2-(N-PG-L-isoleucyloxy)-ethyl iodomethyl carbonate

4-(N-PG-L-isoleucyloxy) butyric acid iodomethyl ester

Iodomethyl-3-(N-PG-L-isoleucyloxy)-propionate

1,3-bis(N-PG-L-isoleucyloxy)-2-propyl 1-iodoethyl carbonate

3-(*N*-PG-L-isoleucyloxy)-2,2-dimethylpropyl iodomethyl carbonate

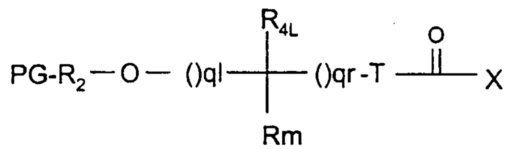
Iodomethyl 2-(N-PG-L-isoleucyloxymethyl)-2-ethyl butyrate,

2-(N-(iodomethoxycarbonyl)-amino)-2-methyl-1-(N-PG-L-isoleucyloxy)-propane, where PG is an N-protecting group.

18 A compound according to claim 17, wherein PG is Boc, Fmoc or especially CBz.

19 A compound according to claim 3, wherein X' is an ether linkage to a Drug bearing an accessible hydroxy function.

20. A compound according to claim 2, with the formula:



wherein

R_{4L} is H, C_{1-3} alkyl or phenyl,

Rm is H, C_{1-3} alkyl, phenyl or $-()_m-O-R_2$

ql is 0-3, qr is 0-3, m is 0-2

T is a bond, $-NR_4-$ or -O-

R_4 is H or C_{1-3}alkyl;

$PG-R_2$ is the acyl residue of an aliphatic amino acid, optionally N-protected.

X is OH, an activating group, an ester linkage to a Drug bearing an accessible hydroxy function, an amide linkage to a Drug bearing an accessible amine function

21. A compound according to claim 20, wherein R_{4L} and Rm are respectively: methyl, methyl;

methyl, hydrogen; or

ethyl, ethyl.

22. A compound according to claim 20 wherein R_{4L} and Rm are H

23 A compound according to claim 20 wherein R_{4L} is H and Rm is

-()m-O-R2.

24 A compound according to claim 20, wherein ql and qr are respectively
1,0;
2,0;
3,0;
4,0.

25 A compound according to claim 20, wherein ql and qr are respectively
1,1;
2,1;
3,1;
4,1; or
2,2.

26 A compound according to claim 20, wherein T is a bond.

27 A compound according to claim 20, wherein T is -NH-.

28 A compound according to claim 20, wherein T is -O-.

29 A compound according to claim 20, wherein PG-R_2 is derived from L-valyl or L-isoleucyl.

30 A compound according to claim 20 wherein X' is halo and PG-R_2 is N-Fmoc-L-valyl, N-Boc-L-valyl, N-CBz-L-valyl, N-Fmoc-L-isoleucyl, N-Boc-L-isoleucyl or N-CBz-L-isoleucyl.

31. A compound according to claim 20 selected from
3-N-PG-valyloxypropanoic acid
4-N-PG-valyloxybutyric acid
4-N-PG-valyloxy cis-but-2-enoic acid
5-N- PG -valyloxypentanoic acid

5-N- PG -valyloxy-cis-pent-2-enoic acid

6-N- PG -valyloxyhexanoic acid

3-N- PG -isoleucyloxypropanoic acid

4-N- PG -isoleucyloxybutyric acid

4-N- PG -isoleucyloxy-cis-but-2-enoic acid

5-N- PG -isoleucyloxypentanoic acid

5-N- PG -isoleucyloxy-cis-pent-2-enoic acid

6-N- PG -isoleucyloxyhexanoic acid,

2,2-dimethyl-3-(N-PG-L-valyloxy)propionic acid

3,3- bis (N-PG-L-valyloxymethyl)-propionic acid,

2-methyl-2-(N-PG-L-valyloxymethyl) propionate,

2-(N-PG-L-valyloxy)-DL-propionate.

2-(N-PG-L-valyloxy)isobutyrate.

2-(N-PG-L-valyloxy)-3-methyl-(S)-(+)-butyrate.

2-O-(N-PG-L-valyloxy)-2-phenyl-DL-acetate

5-(N-PG-L-valyloxy)-2,2-dimethylvalerate

4-(N-PG-L-valyloxy) butyric acid

3-(N-PG-L-valyloxy)-propionate

2-(N-PG-L-valyloxymethyl)-2-ethyl butyrate

2,2-dimethyl-3-(N-PG-L-isoleucyloxy)propionic acid

3,3- bis (N-PG-L-isoleucyloxymethyl)-propionic acid

2-methyl-2-(N-PG-L-isoleucyloxymethyl) propionate,

2-(N-PG-L-isoleucyloxy)-DL-propionate.

2-(N-PG-L-isoleucyloxy)isobutyrate.

2-(N-PG-L-isoleucyloxy)-3-methyl-(S)-(+)-butyrate.

2-(N-PG-L-isoleucyloxy)-2-phenyl-DL-acetate

5-(N-PG-L-isoleucyloxy)-2,2-dimethylvalerate

4-(N-PG-L-isoleucyloxy) butyric acid

3-(N-PG-L-isoleucyloxy)-propionate

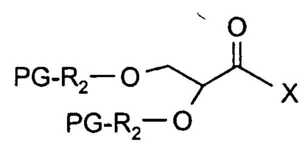
and the corresponding activated acid halides

where PG is an N-protecting group.

32 A compound according to claim 31, wherein the protecting group is Fmoc, Boc or CBz.

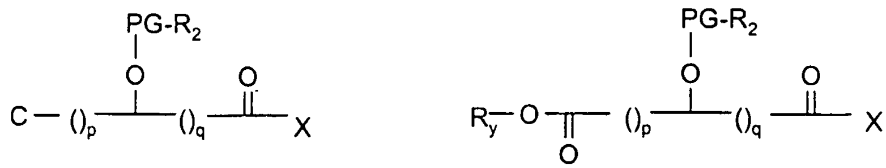
33. A compound according to claim 20, wherein the drug is esterified to
3-valyloxypropanoic acid
4-valyloxybutyric acid
4-valyloxy cis-but-2-enoic acid
5-valyloxypentanoic acid
5-valyloxy-cis-pent-2-enoic acid
6-valyloxyhexanoic acid
3-isoleucyloxypropanoic acid
4-isoleucyloxybutyric acid
4-isoleucyloxy-cis-but-2-enoic acid
5-isoleucyloxypentanoic acid
5-isoleucyloxy-cis-pent-2-enoic acid or
6-isoleucyloxyhexanoic acid

34 A compound according to claim 20 with the structure:



35. A compound according to claim 34 selected from
(R) 2,3-bis-(N-FmocL-valyloxy)-propanoic acid
(R) 2,3-bis-(N-FmocL-isoleucyloxy)-propanoic acid
(R) 2,3-bis-(N-Boc-L-valyloxy)-propanoic acid
(R) 2,3-bis-(N-Boc-L-isoleucyloxy)-propanoic acid
(R) 2,3-bis-(N-CBz-L-valyloxy)-propanoic acid
(R) 2,3-bis-(N-CBzL-isoleucyloxy)-propanoic acid
and the corresponding acid halides.

36 A compound according to claim 20 with the formula:



or

where PG-R_2 is the acyl residue of an aliphatic amino acid, optionally N-protected R_y is H or a carboxy protecting group, p is 0-5, q is 0-5 and X is hydroxy, an activating group or an ester linkage to an hydroxy bearing Drug.

37 A compound according to claim 36 selected from the group consisting of:

2-N-Y-L-valyloxy-L-malic acid

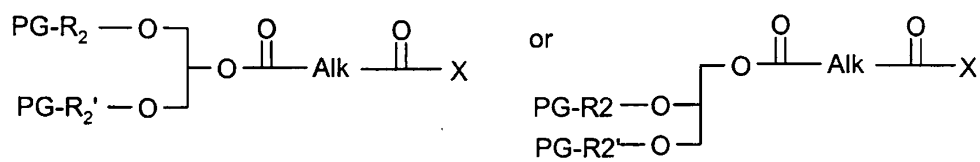
2-N-Y-L-isoleucyloxy-L-malic acid

2-N-Y-L-valyloxy-L-lactic acid

2-N-Y-L-valyloxy-L-lactic acid,

and the corresponding activated acid halides, where Y is Fmoc, Boc or CBz,.

38 A compound according to claim 1, wherein the Linker* $(R_2')_k$-R_2 comprises a structure of the formula:



where Alk is C_1-C_4 alkylene or C_2-C_4 alkenylene and X is OH, an activating group or an ester linkage to the hydroxy bearing Drug.

39 A compound according to claim 38, wherein Alk is methylene or ethylene.

40. A compound according to claim 38, wherein X is OH or an activating group and PG-R_2 and PG-R_2' are N-protected Lvalyl or N-protected L-isoleucyl.

41 A compound according to claim 1, wherein Linker* $(R_2')_k$-R_2 comprises a structure of the formula

$$\text{PG-R}_2\text{—O— ()ql — Ring — ()qr -T}-\overset{\overset{\displaystyle O}{\|}}{C}-X$$

wherein

PG-R_2 is the acyl residue of an aliphatic amino acid, optionally N-protected,

ql is 0-3, qr is 0-3,

T is a bond, -NR_4- or -O-

R_4 is H or C_{1-3}alkyl;

ring is an optionally substituted hetero- or carbocyclic ring structure,

X is OH, an activating group, an ester linkage to a Drug bearing an accessible hydroxy function, an amide linkage to a Drug bearing an accessible amine function or a structure of the formula:

$$-O-\underset{\underset{\displaystyle R_{4R}'}{|}}{\overset{\overset{\displaystyle R_{4R}}{|}}{C}}-X'$$

where

R_{4R} and R_{4R}' are independently H, C_{1-3} alkyl or phenyl; and

X' is halo or an ether linkage to a drug bearing an accessible hydroxy function or an ester linkage to a Drug bearing an accessible carboxy function; and pharmaceutically acceptable salts thereof.

42. A compound according to claim 41, wherein R_{4R} and R_{4R}' are hydrogen.

43 A compound according to claim 41, wherein R_{4R} and R_{4R}' are methyl.

44 A compound according to claim 41, wherein R_{4R} is H and R_{4R}' is methyl..

45 A compound according to claim 41, wherein, the optional substituent to ring is PG-R_2-O-($)_m$- where m is 0-2.

46 A compound according to claim 41 wherein ring is phenyl, cyclobutyl, cyclopentyl, cyclohexyl, furyl or pyridyl.

47 A compound according to claim 41, wherein ql and qr are respectively:
1,0;
2,0;
3,0;
4,0;

48 A compound according to claim 41, wherein ql and qr are respectively:
1,1;
2,1;
3,1;
4,1; or
2,2.

49 A compound according to claim 41, wherein T is a bond.

50 A compound according to claim 41, wherein T is -NH-.

51 A compound according to claim 41, wherein T is -O-.

52 A compound according to claim 41, wherein PG-R_2 is derived from L-valyl or L-isoleucyl.

53 A compound according to claim 52 wherein X' is halo and PG-R_2 is N-Fmoc-L-valyl, N-Boc-L-valyl, N-CBz-L-valyl, N-Fmoc-L-isoleucyl, N-Boc-L-isoleucyl or N-CBz-L-isoleucyl.

54 A compound according to claim 52 selected from
Iodomethyl 4-(N-PG-L-valyloxy) benzoate.
Iodomethyl-3-(N-PG-L-valyloxy)-benzoate
Iodomethyl 3,4-di-(N-PG-L-valyloxy)hydrocinnamate
3-(N-PG-L-valyloxy)phenyl iodomethyl carbonate
Iodomethyl 2-(N-PG-L-valyloxy)phenylacetate
Iodomethyl 4-(N-PG-L-valyloxyxy)phenylacetate
Iodomethyl 4-(2-N-PG-L-valyloxyethyl) benzoate
Iodomethyl 4-(N-PG-L-valyloxy)cyclohexanoate
1-(2-N-PG-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester
Iodomethyl 5-[(*N*-PG-L-valyloxy)methyl]-2-furoate
Iodomethyl 4-(2-N-PG-L-valyloxyethoxy)-benzoic acid
Iodomethyl 4-(N-PG-L-isoleucyloxy) benzoate.
Iodomethyl 3,4-di-(N-PG-isoleucyloxy)hydrocinnamate
3-(N-PG-L-isoleucyloxy)phenyl iodomethyl carbonate
Iodomethyl 2-(N-PG-L-isoleucyloxy)phenylacetate
Iodomethyl 4-(N-PG-L-isoleucyloxy)phenylacetate
Iodomethyl 4-(2-N-PG-L-isoleucyloxyethyl) benzoate
Iodomethyl 4-(N-PG-L-isoleucyloxy)cyclohexanoate,
1-(2-N-PG-isoleucyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid iodomethyl ester
iodomethyl 5-[(*N*-PG-L-isoleucyloxy)methyl]-2-furoate
iodomethyl 4-(2-N-PG-L-isoleucyloxyethoxy)-benzoic acid
wherein PG is an N-protecting group

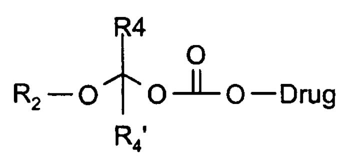
55 A compound according to claim 54 wherein PG is Fmoc, Boc and especially CBz.

56 A compound according to claim 41, selected from the group:

4-(N-PG-L-valyloxy) benzoate.
3-(N-PG-L-valyloxy)-benzoate
3,4-di-(N-PG-L-valyloxy)hydrocinnamate
2-(N-PG-L-valyloxy)phenylacetate
4-(N-PG-L-valyloxyxy)phenylacetate
4-(2-N-PG-L-valyloxyethyl) benzoate
4-(N-PG-L-valyloxy)cyclohexanoate
1-(2-N-PG-L-valyloxyethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid
5-[(*N*-PG-L-valyloxy)methyl]-2-furoate
4-(2-N-PG-L-valyloxyethoxy)-benzoic acid
4-(N-PG-L-isoleucyloxy) benzoate.
3,4-di-(N-PG-isoleucyloxy)hydrocinnamate
2-(N-PG-L-isoleucyloxy)phenylacetate
4-(N-PG-L-isoleucyloxy)phenylacetate
4-(2-N-PG-L-isoleucyloxyethyl) benzoate
4-(N-PG-L-isoleucyloxy)cyclohexanoate,
1-(2-N-PG-isoleucyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid
5-[(*N*-PG-L-isoleucyloxy)methyl]-2-furoate
4-(2-N-PG-L-isoleucyloxyethoxy)-benzoic acid
wherein PG is an N-protecting group

57 A compound according to claim 56 wherein PG is Fmoc, Boc and especially CBz.

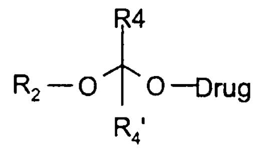
58. A compound according to claim 1 with the structure:



where R_4 and R_4' are independently H or C_{1-3} alkyl and the Drug bears an accessible hydroxy function

59 A compound according to claim 58, wherein linker*$(R_2')_k$-R_2 is a derivative of L-valyloxymethylcarbonate or L-isoleucyloxymethylcarbonate.

60 A compound according to claim 1 with the structure

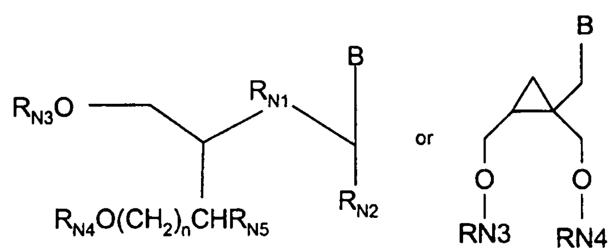


where R_4 and R_4' are H or C_{1-3} alkyl and the Drug has an accessible carboxy or hydroxy function.

61 A compound of the formula 60, wherein linker*$(R_2')_k$-R_2 is an L-valyloxymethyl ether, L-valyloxymethyl ester or L-isoleucyloxymethyl ether or L-isoleucyloxymethyl ester.

62. A compound according to claim 1, wherein the Drug is a di- or trihydric nucleoside analogue, an NNRTI, an HIV protease inhibitor, a peptidomimetic or oligopeptide, levodopa, cromolyn, an opiate, an antibacterial glycopeptide, a rifamycin, a cephalosporin, a tacrine, carvedilol, a statin, etoposide or a taxol.

63. A compound according to claim 62 wherein the nucleoside analogue has the formula:



where B is a natural or unnatural nucleotide base,

R_{N1} is O or -CH_2- or S

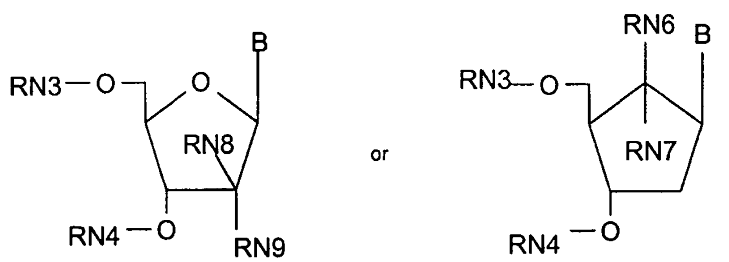
R_{N2} and R_{N3} are each H or R_{N2} is methylene or -CH(OH)- and R_{N3} is a bond thereto, or R_{N2} and R_{N3} together are a bond;

n is 0 or 1;

one of R_{N3} and R_{N4} comprises a linker*-$(R_2)_k$-R_2 structure

64 A compound according to claim 63, wherein the linker*-$(R_2)_k$-R_2 structure ia attached to the (nominal) 5' hydroxy.

65 A compound according to claim 62, where the nucleoside analogue has the formula:



where B, RN3 and RN4 are as defined in claim 52 and

RN6 is fluoro and RN7 is hydrogen or RN6 and RN7 are both fluoro or RN6 and RN7 together define an exo-methenyl group

RN8 and RN9 are fluoro (or one of them is fluoro and the other is hydrogen) or RN8 and RN9 together define exomethenyl or exomethenyl mono or di-subsituted with fluoro.

66 A compound according to claim 62 wherein the nucleoside analogue is selected from ribavirin, Ara A, Ara G, Ara C, 1592U89, lobucovir, BMS 200 475 (9-[2-methylen-3-hydroxymethyl-4-hydroxycyclopentyl]guanine, H2G, pencicovir, ganciclovir and 9-[2,3-(trans)dihydroxymethylcyclobutyl]guanine.

67 Use of a structure of the formula

$$\text{linker}^*(R_2')_k\text{-}R_2$$

as defined in claim 1 as a prodrug moiety for a pharmaceutical compound bearing an accesible hydroxy, amine or carboxy function, wherein either

a structure of the formula linker*(N-PG-R_2')$_k$-N-PG-R_2 where N-PG is an N-protecting group is attached to said accessible function; or wherein the the linker* moiety is first attached to the accessible function and the R_2 group(s) are then attacehd thereto.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00194

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07K 5/00, C07D 473/32, C07D 473/00, C07H 19/16, C07D 501/34, C07D 211/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07K, C07D, C07H, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9424134 A1 (HOECHST AKTIENGESELLSCHAFT), 27 October 1994 (27.10.94) --	1-67
A	WO 9730051 A1 (MEDIVIR AB), 21 August 1997 (21.08.97) --	1-67
A	EP 0375329 A2 (THE WELLCOME FOUNDATION LIMITED), 27 June 1990 (27.06.90) --	1-67
P,A	WO 9821223 A1 (MEDIVIR AB), 22 May 1998 (22.05.98) --	1-67

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" erlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 1999	13 -06- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00194

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 2112057 A (LOEVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB), 23 Sept 1971 (23.09.71)	1-67
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00194

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-16, 19-30, 36, 38-53, 58-67
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

The formulation of the claims is so complicated, owing to the very wide range of combinations of variable parts, that PCT Article 6 is no longer complied with. This Article specifies that the claims must be formulated in a clear and concise manner. The search has therefore been limited to compounds with the same or similar structure as claimed having the same or similar effects as mentioned int the description.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/05/99

International application No.
PCT/SE 99/00194

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